TEMPORAL PATTERNS OF HEART RATE AND RHYTHM, STROKE VOLUME, AND CARDIAC OUTPUT IN CRITICALLY ILL ADULTS IN A CARDIAC SURGICAL INTENSIVE CARE UNIT

by

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TABLE OF CONTENTS

TABLE OF CONTENTS (continued)

TABLE OF CONTENTS (continued)

TABLE OF CONTENTS (continued)

LIST OF TABLES

LIST OF TABLES (continued)

LIST OF TABLES (continued)

LIST OF FIGURES

LIST OF FIGURES (continued)

LIST OF FIGURES (continued)

LIST OF FIGURES (continued)

CHAPTER I

STATEMENT OF THE PROBLEM

Rhythmicity is a common phenomenon in nature. A rhythm, which is synonyomous with an oscillation or cycle, is a sequence of events that repeats itself through time in the same order and at the same interval (Minors & Waterhouse, 1981). Rhythmicity is seen in the seasons of the year, phase of the moon, day and night rotation of the earth, and twice daily ebb and flow of the tides (Kleitman, 1963). Plants and animals have evolved to respond in a rhythmic manner in order to live, grow, and reproduce. Rhythmic activity is a fundamental property of living organisms (Reinberg & Smolensky, 1983).

For most living organisms, the most evident environmental rhythm is the alternation between day and night (Minors & Waterhouse, 1981). Corresponding to this environmental rhythm, many human physiological and psychological processes oscillate with a frequency of about 24 hours. The observed rhythms of these processes are self-generated within the body and are influenced both by an internal timekeeping system (endogenous component) and by individual person characteristics and environmental factors outside the body's timekeeping system (exogenous component). The characteristic of possessing endogenous rhythmicity (being able to self-generate a rhythm) is termed periodicity. The body's timekeeping system is synchronized or entrained by individual person characteristics and environmental factors to a period of 24 hours. Some time cues are behaviors or habits that follow a rhythmic, day-night, 24-hour routine, such as, activity and rest, sleep and wakefulness, eating and fasting, drinking and abstaining, and work and leisure (Conroy & Mills, 1970). Other

time cues may be noise, smells, ambient air temperature, and social events or contacts (Wever, 1979; Reinberg & Smolensky, 1983).

When humans are isolated from all external environmental time cues, many self-generated rhythms continue in a free-running state close to 24 hours (ranging from 20-28 hours)(Moore-Ede, Sulzman, & Fuller, 1982). Thus, the internal timekeeping system continues to time the rhythms to a period close to 24 hours without external input. When a rhythm oscillates with a frequency of about 24 hours (20-28 hours), it is called a circadian rhythm (Minors & Waterhouse, 1981). Circadian is derived from the latin circa for "about" and dies for "day" (Halberg, 1959).

Many physiological variables have been found to have circadian rhythms. Some variables have a strong endogenous component (e.g. body temperature), while others, have a weaker endogenous component with a strong exogenous component (e.g. blood pressure, heart rate, and cardiac output). The observed rhythm of rhythmic variables in natural environmental conditions is a combination of the endogenous rhythmicity of the variable and the effect of influences on the variable that are exogenous to the timekeeping system.

A temporal variation in heart rate has been recognized since the second century in the writings of the Greek physician, Galen. However, a 24-hour rhythm in heart rate was not demonstrated until the 19th century (Guy, 1839). During the last 50 years, numerous studies have documented circadian, ultradian (period of less than 20 hours), or infradian (period greater than 28 hours) rhythms in selected cardiovascular variables (cardiac output, stroke volume, heart rate, arterial blood pressure, blood flow, capillary resistance, blood

volume, and plasma volume) (Kleitman & Ramsaroop, 1948; Smolensky et al., 1976a).

Over a hundred studies have demonstrated that heart rate has a circadian rhythm in normals and in inpatients and outpatients with a variety of diseases. (Menzel, Timm, & Herrnring, 1949; Kuzel, 1973; Smolensky, Bergman, Barnard, Beck, & Kraft, 1977). Felver and Hoeksel (1990) have found circadian and ultradian rhythms in patients in a medical intensive care unit (ICU). Kuzel (1973) has shown that heart rate and selected arrhythmias [premature atrial beats (PACs), premature ventricular beats (PVCs), and junctional escape beats] have circadian and ultradian rhythms in patients with myocardial infarction in an ICU. Many other studies have confirmed a circadian or an ultradian rhythm in selected heart rhythms in normals and in patients (Domenichelli et al., 1980; Sensi et al., 1980; Tartini, Moccetti, Riva, & Belli, 1980; Leach, Ruskin, & Halberg, 1981; Orth-Gomer et al., 1982; Leach, Ruskin, Halberg, & Sothern, 1983; DeScalzi et al., 1984; DeLeonardis, DeScalzi, Fabiano, & Cinelli, 1985).

Ten studies with small numbers of subjects have described the daily variation in stroke volume or cardiac output or both. Stroke volume is the volume of blood the heart ejects from the ventricle with each heart beat. Cardiac output is the product of stroke volume and heart rate. These variables have been found to have circadian rhythms in healthy subjects and in stable patients (Kroetz, 1940; Kaiser & Maurath, 1949; Schroder et al., 1969; Smolensky et al., 1976a). Adamian, Aslanian, and Grigorian (1984) found a circadian rhythm in cardiac output and stroke volume in a sample of 141 patients with coronary heart disease and in 26 healthy subjects. Miller and

coronary heart disease and in 26 healthy subjects. Miller and Helander (1979) found that cardiac output decreased during the night when subjects normally slept even when they stayed awake.

Most of the studies of periodic variation in cardiovascular variables have been done in healthy people of all ages. The majority of the investigators who did not include normals, included people with stable medical problems. Few studies have described the daily variation in cardiovascular variables in acutely ill, hospitalized patients and even fewer have described these variations in critically ill patients in ICUs.

The internal environment of the critically ill patient is constantly changing in response to illness and treatment, and the external environment of the ICU is unfamiliar, disruptive, and inconsistent. The overall physiological reaction of patients to their internal and external environments may be wide fluctuations in measured cardiovascular variables. Even if the rhythms of these variables continue in the disruptive ever changing ICU environment, they may be masked by "biological noise."

Some patients in ICU have been shown to have circadian and ultradian rhythms in heart rate and selected heart rhythms (Kuzel, 1973; Felver & Hoeksel, 1990). No prior study of these rhythms could be found for cardiac output and stroke volume in patients in the ICUs.

Nursing therapies that affect the patient's hemodynamics could be timed more appropriately if the daily fluctuations in these cardiovascular variables were known. For example, knowing when a patient's cardiac output was lowest or highest during the day would provide rationale for timing an intervention that changes cardiac

guide timing of antiarrhythmic therapy. Knowledge of baseline fluctuation in these variables in critically ill adults is necessary in planning and critiquing research using these variables in critically ill adults. Nursing research could be planned that would determine the effect of altering the patient's external environment (lights, noise, meals, social cues, etc.) on the observed rhythm of physiological variables.

No study could be found that described the daily variation in heart rate and rhythm, stroke volume, and cardiac output measured simultaneously. No documentation could be found that described the variation in stroke volume and cardiac output related to time of day in critically ill adults in an ICU. If daily variations in these variables could be identified, characterizing their nature in critically ill patients would be useful to nursing. Knowing the characteristics of fluctuations in these variables would be useful to define the limits of their ranges in relation to an individual's circadian rhythm and would provide explanatory value in understanding these patients' vital signs clinically and in research settings. The goal of this research is to describe the temporal pattern of heart rate and rhythm, stroke volume, and cardiac output in critically ill adults in an ICU.

CHAPTER II

REVIEW OF LITERATURE AND CONCEPTUAL FRAMEWORK

To provide a basis for understanding observed biological rhythms seen in humans, this chapter discusses predictive and reactive homeostasis, traces the development of the science of chronobiology, and describes the conceptual framework used in the study. The physiology and measurement of heart rate and rhythm, stroke volume, and cardiac output are discussed and the literature about the rhythmicity of these variables is reviewed. The critically ill adult and the environment of the ICU are described. The chapter concludes with a summary and a statement of the purpose of the study.

Homeostasis

Over 60 years ago, Walter B. Cannon formulated the concept of homeostasis. Homeostasis is the tendency of living organisms to maintain their internal equilibrium by the use of specialized mechanisms that respond to changes in environmental conditions (Moore-Ede, 1986). Cannon suggested that physiological variables were free to oscillate within a normal circumscribed range and that this was why he chose "homeo" (similar) instead of "homo" (same) for the term homeostasis (Cannon, 1929). Figure 1 demonstrates how Cannon applied the concept of homeostasis to maintenance of blood glucose. Blood glucose varies within narrow limits and is maintained within these limits by homeostatic mechanisms. The fluctuations within this range were shown as a regular rhythm. Moore-Ede (1986) expanded the concept of homeostasis to include precisely timed mechanisms that enable the living organism to predict environment challenges in advance and begin responding before the challenges actually occur. Moore-Ede termed the

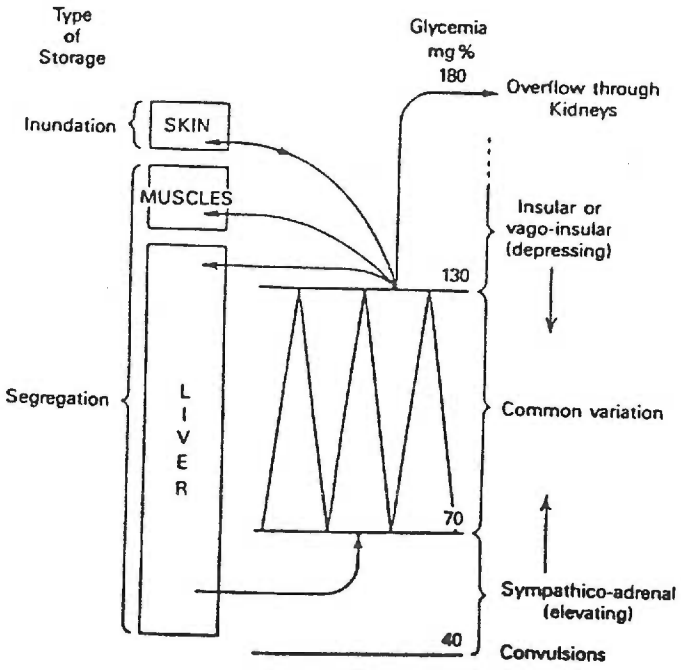


Figure 1. Cannon's first illustration used to explain the concept of homeostasis. Blood glucose is maintained between upper and lower limits, but is free to oscillate within those limits. From "Organization for Physiological Homeostasis," by W.B. Cannon, 1929, Physiological Reviews, 9(3), p. 410, as reproduced by "Physiology of the Circadian Timing System: Predictive Versus Reactive Homeostasis," by M. C. Moore-Ede, 1986, The American Journal of Physiology, 250, p. R738. Copyright 1986 by The American Physiological Society. Reprinted by permission.

original concept of homeostasis (corrective actions the body takes in response to a change that has already occurred) reactive homeostasis and called responses initiated in anticipation of a predictably timed challenge, predictive homeostasis. Predictive homeostasis provides an advantage to the organism by activating mechanisms that require time to execute in advance of the normal stimuli. Thus, the organism is maximally prepared when needed. The probability the occurrence of specific challenges is highly related to specific phases of stable environmental cycles (i.e. day and night cycle, seasons of the year). A timekeeping system has evolved within living organisms that can both measure time precisely and reset itself over time. Thus, the expanded concept of homeostasis provides a basis for understanding the overt rhythms seen in human beings.

Chronobiology

Chronobiology is a branch of biological science that is concerned with the mechanisms and alterations of each organism's temporal structure under various situations (Halberg, Carandente, Cornelissen, & Katinas, 1977). Appendix A contains a glossary of terms commonly used in the chronobiology literature. Figure 2 illustrates different forms of a rhythm. A rhythm can be either sinusoidal, symmetrical but not sinusoidal, or asymmetrical. A cycle can be measured from one peak to the next, or one trough to the next. A period is the duration of time of one cycle. Parameters used to describe biological rhythms are acrophase, amplitude, and mesor. When a cosine curve with a fixed-time period is fitted to a rhythmically oscillating variable the peak value is termed the acrophase. It is usually expressed in clock hours (e.g. referenced to midnight) or may be referenced to

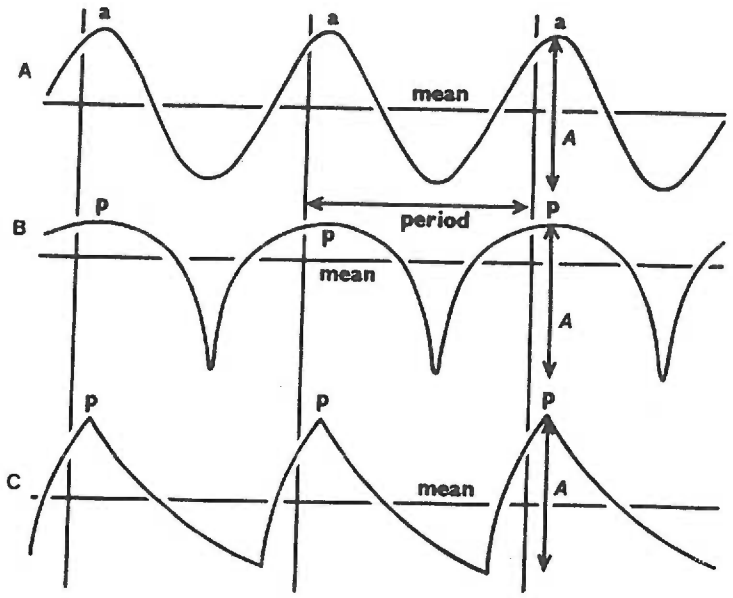


Figure 2. Different forms of a rhythm. (A) Sinusoidal (B) Symmetrical but non-sinusoidal (C) Asymmetrical. a = acrophase; P = peak; A = peak to trough amplitude. The vertical lines divide the traces up into two cycles. Adapted from Human Circadian Rhythms (p. 2) by R. T. Conroy and J. N. Mills, 1970, London: J. & A. Churchill.

sleep or awakening. Acrophase may be expressed in hours or as degrees of arc (Mills, 1973). One half of the total regular excursion of a fitted cosine wave is commonly called the amplitude. In this study, the term half-amplitude will be used to describe one half of the total excursion. The mesor (Midline Estimate Statistic of Rhythm) is the mean of the cosine curve fitted to the rhythmic variable (Mills, 1973).

Biological systems have a prominent temporal structure. Many biological rhythms have a time period of about 24 hours (20-28 hours) and are termed circadian. Other rhythms have a period of less than 20 hours (ultradian) or period greater than 28 hours (infradian) Circadian and circannual (1 year) biological rhythms have been documented in many physiological variables in plants and animals. ". . . circadian rhythms appear to be related to the daily rotation of the Earth around its axis . . .; similarly, circannual rhythms appear to be related to the rotation of the Earth around the Sun" (Reinberg & Smolensky, 1983, p. 2).

Biological rhythms were reported by Greek and Roman scholars. For centuries it was thought that cyclic changes in organisms were the result of cyclic changes in environmental factors such as day-night alternation and ambient air temperature change within 24 hours and within one year (Reinberg & Smolensky, 1983). In 1729, the exogenous origin of biological rhythms in plants was demonstrated by de Mairan, who found that the leaf position of the heliotrope continued to change daily in constant darkness. Similarly, in the late 19th and early 20th centuries, Pfeffer found that circadian rhythms in leaf movement in plants continued in constant darkness (Reinberg & Smolensky, 1983).

De Candolle (1832) documented that circadian rhythms persisted in constant conditions with a time period differing from 24 hours. The leaf movement of the Mimosa pudica continued in constant darkness with a period of 22 to 23 hours. Bunning (1935) demonstrated that the bean plant had a circadian rhythm in leaf movement and that this rhythm was transmitted genetically. Bunning (1963) also found that plants have an endogenous mechanism to measure time.

Animal and plant cells are genetically programmed to reach maximum activity at an exact phase of their circadian rhythm. Thus, an organism's ability to respond efficiently depends on the particular phase of the period which it is in (Reinberg & Smolensky, 1983).

Much previous and current work has focused on identifing and describing the body's internal timekeeping system. The suprachiasmatic nuclei of the hypothalamus in animals, including humans are thought to be a major synchronizer of circadian oscillations (Wilkinson, 1989). Without this synchronizor, some ultradian and circadian rhythms continue but they may not be timed with each other (Reinberg & Smolensky, 1983).

In 1954, environmental rhythms were found to synchronize and entrain circadian rhythms (Aschoff, 1954). These environmental factors are called zeitgebers (time givers) (Aschoff, 1954). One of the most powerful zeitgebers in plants and animals is the 24-hour alternation of day and night (Reinberg & Smolensky, 1983). Halberg and coworkers have found that the most powerful zeitgeber in humans is cyclic changes in socioecological factors (F. Halberg, E. Halberg, Barnum, & Bittner, 1959).

In 1960, cosinor analysis was introduced as an objective,

statistical approach for detecting, describing, and quantifying biological rhythms (Pittendrigh, 1960). Cosinor is the merger of the terms "cosine" and "vector" to highlight the vectorial aspects of the acrophase and rhythm amplitude. A detailed description of cosinor analysis can be found in the glossary in Appendix A.

With cosinor analysis, the least squares regression method is used to determine the best fitting cosine function for approximating time series data with a known period length. The function is as follows:

$$y\ (t_i) = M + A \cos\ (\omega t_i + \phi)$$

where t_i = time; A = half-amplitude; ϕ = acrophase; ω = angular frequency ($\omega = 2\pi/\tau$, where τ = period and $1/\tau$ = frequency). This technique provides point estimates of the rhythmic parameters to characterize the rhythm: period (τ), time of the crest, or acrophase (ϕ), the half-amplitude (A), and the mesor (M). Cosinor analysis provides a test of goodness of fit of the sinusoidal model with a fixed-period length that is determined a priori. In single cosinor analysis, time-series data from one individual (serially dependent data) is used. In group cosinor analysis, time-series data from individuals is combined. Cosinor analysis tests the hypothesis that the half-amplitude of the rhythm is equal to zero using the F test. The R^2 values indicates how much variance in the variable of interest is explained by having the cosine function in the equation. The cosinor method can be used several times, using different and multiple periods to detect harmonics (Reinberg & Smolensky, 1983).

Since the advent of cosinor analysis, many studies have demonstrated ultradian, circadian, and circannual rhythms in many

biological functions of practically every species (Minors & Waterhouse, 1986). It is now recognized that rhythmicity is a fundamental property of all living things (Reinberg & Smolensky, 1983).

Chronobiology applied to health care can be seen in the fields of chronopathology, chronotoxicology, chronopharmacology, chrononutrition, and chronotherapy. All of these sciences use the concepts of chronobiology to identify phases of resistance and susceptibility to insult in order to time interventions to obtain maximal effects.

Conceptual Framework

The conceptual framework used for this study describes the relationship between the overt rhythms in biological variables and factors that influence the observed pattern (overt rhythm). Figure 3 illustrates this relationship and indicates potential areas for nursing intervention.

Overt rhythms observed when normal cycles of the solar day are present are the result of both endogenous self-generated rhythms (synchronized by the body's internal timekeeping system) and other influences. The body's timekeeping system is entrained by internal and external environmental factors. These same influences, that are external to the timekeeping system, also can directly affect the variable being measured. Examples of these influences are reactive homeostatic responses related to illness and transient stimuli related to medications or treatments. Figure 4, details other examples of individual patient characteristics and time cues and transient stimuli in the environment that affect the overt rhythm directly or by way of

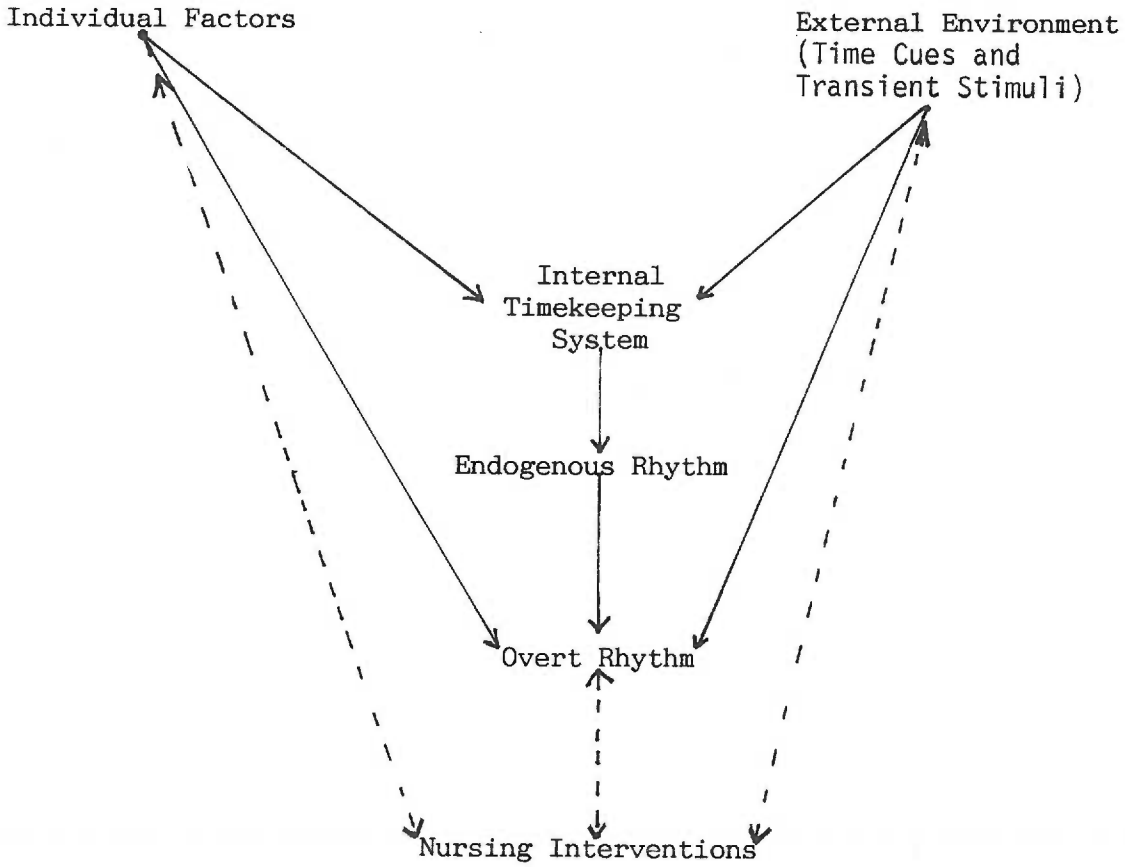


Figure 3. Conceptual framework

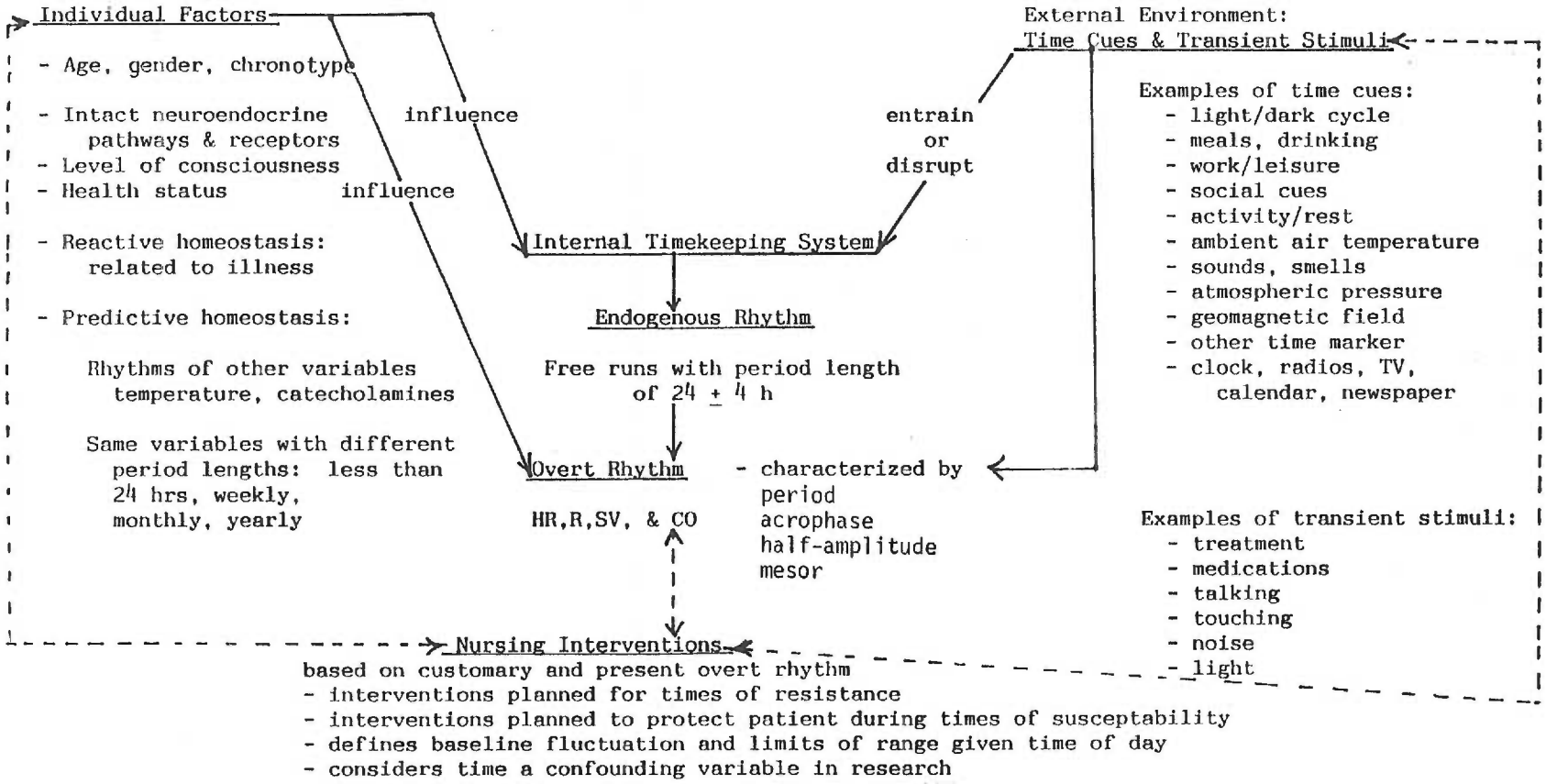


Figure 4. Detailed conceptual framework

the internal body's timekeeping system.

Entrainment of Endogenous Rhythms

Endogenous rhythms are synchronized by the body's internal timekeeping system to a period of about 24 hours (20-28 hours)(Minors & Waterhouse, 1986). The suprachiasmatic nuclei in the area of the hypothalamus have been found to be responsible for synchronizing many circadian rhythms, although, other sites probably participate. As seen in Figure 5, the suprachiasmatic nuclei are anterior and superior to the optic chiasma. If the suprachiasmatic nuclei are destroyed in experimental animals, many ultradian and circadian rhythms continue, but they become asynchronous with each other.

Environmental rhythms are known to affect the timekeeping system. The daily alternation of day and night is a major influence. Others include activity and rest, sleep and wakefulness, eating and fasting, drinking and abstaining, work and leisure, noise, smells, and social cues and interactions (Conroy & Mills, 1970; Wever, 1979; Reinberg & Smolensky, 1983). These environmental time cues entrain, or synchronize, the internal timekeeping system which, in turn, synchronizes the endogenous rhythms. The timekeeping system can be entrained by time cues to a period of exactly 24 hours.

When a person is kept in constant conditions or in conditions with no external time cues, most circadian rhythms continue to oscillate with a period close to, but not exactly 24 hours. Thus, the innate period of an endogenous rhythm is not exactly 24 hours and its length is controlled without external time cues by an internal timekeeping system. Within individuals, the "free-running" rhythms have a stable, repeating period (Minors & Waterhouse, 1986). Some

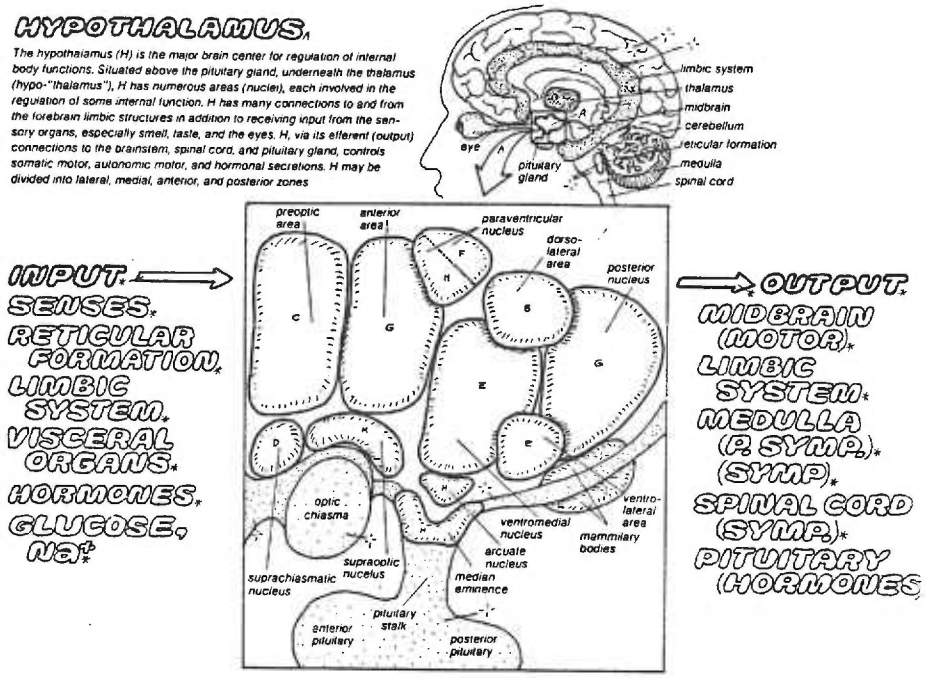


Figure 5. Location of the suprachiasmatic nuclei of the hypothalamus (D). From The Physiology Coloring Book (p. 102) by W. Kapit, R. I. Macey, and E. Meisami, 1987, New York: Harper and Row. Copyright 1987 by Wynn Kapit, Inc., Robert I. Macey, and Esmail Meisami. Reprinted by permission.

individuals have a short free-running period (less than 24 hours) and some a long free-running period (greater than 24 hours). This difference in free-running periods may be in part what causes the characteristic tendency of "morningness" or "eveningness" in some individuals (Kerkhof, 1985). This characteristic is called chronotype.

Other Influences

An age-related reduction of rhythm amplitude has been observed in many circadian rhythms (Kerkhof, 1985). Environmental rhythms and many other environmental factors also affect the overt rhythm directly. In addition, internal adaptation to stress and illness (reactive homeostasis) and biological rhythms of other variables directly affect overt rhythms. For example, sleep and wakefulness have a very strong exogenous effect on an overt rhythm. These exogenous influences can mask the underlying endogenous rhythm. Exogenous influences can also affect the timekeeping system itself (Minors & Waterhouse, 1986). Figure 6 illustrates the combined effect of these influences on an overt temperature rhythm. Figure 7 illustrates the endogenous and exogenous components of an overt rhythm that has been entrained by zeitgebers to a 24-hour period. Some biological rhythms are influenced more endogenously (e.g. body temperature) while others are influenced more exogenously by individual person characteristics and environmental factors external to the timekeeping system (e.g. heart rate, blood pressure). Thus, the overt or observed rhythm is the result of both exogenous and endogenous influences.

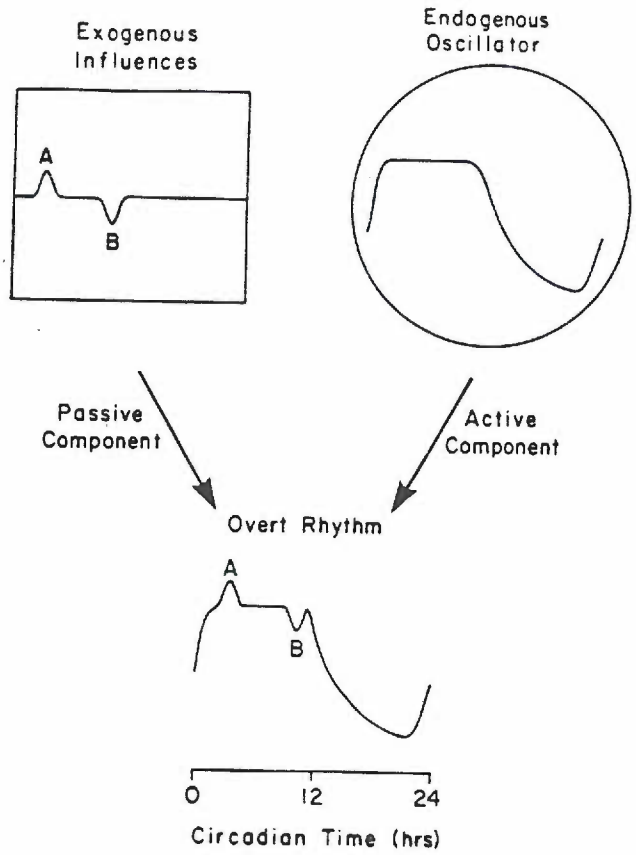


Figure 6. The contributions of exogenous influences and endogenous oscillations to an overt rhythm such as body temperature. Left, A represents an increase in body temperature due to a hot shower in the morning and B represents a drop in body temperature due to eating a liter of ice cream. These passive components will change body temperature whenever they occur. Right, the rhythmic pattern of body temperature as timed by endogenous circadian oscillators. Below, the measured overt rhythm reflects both the endogenous rhythm and the exogenous influences. From The Clocks That Time Us (p. 28) by M. C. Moore-Ede, F. M. Sulzman, and C. A. Fuller, 1982, Cambridge, Massachusetts: Harvard University Press. Copyright 1982 by The President and Fellows of Harvard College. Reprinted with permission.

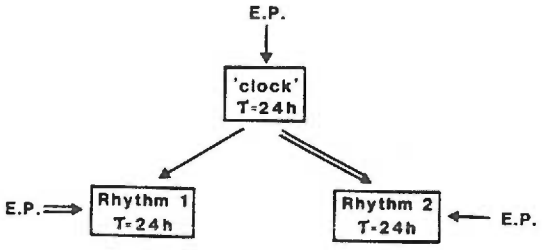


Figure 7. Influences on an overt rhythm. Rhythms result from an interaction of endogenous and exogenous influences. E.P. = external periodicities which oscillate with a period of 24 hours, τ = period, ⇒ indicates dominant influence and → indicates weak influence. From Circadian Rhythms and the Human (p. 9) by D. S. Minors & J. M. Waterhouse, 1981, Boston, John Wright & Sons, Inc. Copyright 1981 by Dr. D. S. Minors and Dr. J. M. Waterhouse, Department of Physiology, Stopford Building, University of Manchester, Manchester, M13 9PT. Adapted by permission.

Heart Rate and Rhythm, Stroke Volume, and Cardiac Output

Definitions and Normal Values

Heart rate is the number of times the heart contracts per minute, and stroke volume is the amount of blood ejected by the heart with each contraction. In the adult, the resting heart rate normally ranges from 60 to 100 beats per minute, and stroke volume ranges from 60 to 130 ml per heart beat (Grossman, 1986). Cardiac output is defined as the amount of blood ejected from the heart per unit of time and is the product of stroke volume and heart rate. Thus, for example:

Cardiac Output = Stroke Volume x Heart Rate

= 60 ml/beat x 70 beats/minute

= 4.2 liters/minute

In the adult, the normal range of cardiac output is 4-8 liters/min.

Because cardiac output and stroke volume are proportional to the body surface area (BSA), they are often expressed as indexed to BSA. Cardiac index and the stroke index are obtained by dividing cardiac output and stroke volume respectively. Using the Dubois and Dubois (1916) weight-height equation, BSA is obtained as follows:

$BSA\ (m^2) = 0.007184 \times \text{Lean Body Weight (kg)}^{0.425} \times \text{Height (cm)}^{0.725}$

In the adult, the normal range for the cardiac index is 2.5-4 $l/min/m^2$ and the mean stroke index is 46 $ml/beat/m^2 \pm 8.1$. (Yang, Bentivoglio, Maranhao, & Goldberg, 1988).

In the normal adult, heart rate and stroke volume and therefore cardiac output, decrease with age. Brandfonbrener and coworkers measured a 1% decrease in cardiac output per year after age 35. The values for each decade are shown in Table 1. Note that

Table 1

Mean Normal Values for Heart Rate, Cardiac Output, and Stroke Volume as a Function of Age

	Age (yr)	No. of subjects	BSA (m^2)	HR (beats/min)	CO (l/min)	SV (ml/beat)
	23.6	9	1.75	76.9 ± 4.6	6.49 ± 0.51	85.6 ± 6.1
	34.1	10	1.86	71.7 ± 3.4	6.57 ± 0.56	91.8 ± 7.1
	43.3	11	1.81	69.1 ± 3.0	5.34 ± 0.32	78.3 ± 4.7
	54.8	11	1.67	69.8 ± 2.8	4.63 ± 0.21	67.2 ± 3.1
	65.4	10	1.67	63.0 ± 3.2	4.29 ± 0.28	69.5 ± 4.9
	73.3	9	1.61	65.8 ± 3.6	4.05 ± 0.25	63.0 ± 4.7
	82.0	7	1.64	67.0 ± 7.5	3.87 ± 0.39	60.1 ± 5.1
Mean ± SD	52.5	67	1.72	69.1 ± 12.1	5.08 ± 1.51	74.2 ± 18.9

Data from "Changes in Cardiac Output with Age" by M. Brandfonbrener, M. Landowne, & N. W. Shock, 1957, Circulation, 12, p. 561. Values are means ± 1 standard deviation. BSA, body surface area; HR, heart rate; CO cardiac output; and SV, stroke volume.

circadian variation was not considered (Brandfonbrener, Landowne, & Shock, 1957).

Determinants of Cardiac Output

Figure 8 illustrates the major interacting factors that determine cardiac output through their effects on heart rate and stroke volume. Heart rate is affected by the nervous system as well as the endocrine system. An increase or decrease in heart rate is the result of activation or suppression of these systems in response to internal and external stimuli. Heart rate itself can also affect stroke volume by altering diastolic filling of the heart. With a rapid heart rate, diastolic filling time and left ventricular end-diastolic volume (preload) are reduced; in contrast with a slow heart rate, diastolic-filling time and preload are increased. If the heart rhythm is irregular, stroke volume is not constant from beat to beat. With some arrhythmias, such as atrial fibrillation, the atria beat irregularly at a rate of over 400 per minute and do not contract at all. If the atria do not contract, then ventricular filling and preload are reduced.

Stroke volume is also affected by four other factors in addition to heart rate: ventricular end-diastolic volume (preload), resistance the left ventricle must overcome to open the aortic valve and eject blood from the heart (afterload), ability of the myocardial fibers to shorten and develop tension under constant load (contractility), and ability of the myocardium to contract in a coordinated synchronized way (synergy of contraction).

As preload increases, stroke volume increases because myocardial fibers are stretched to a certain maximum. After a certain point, any

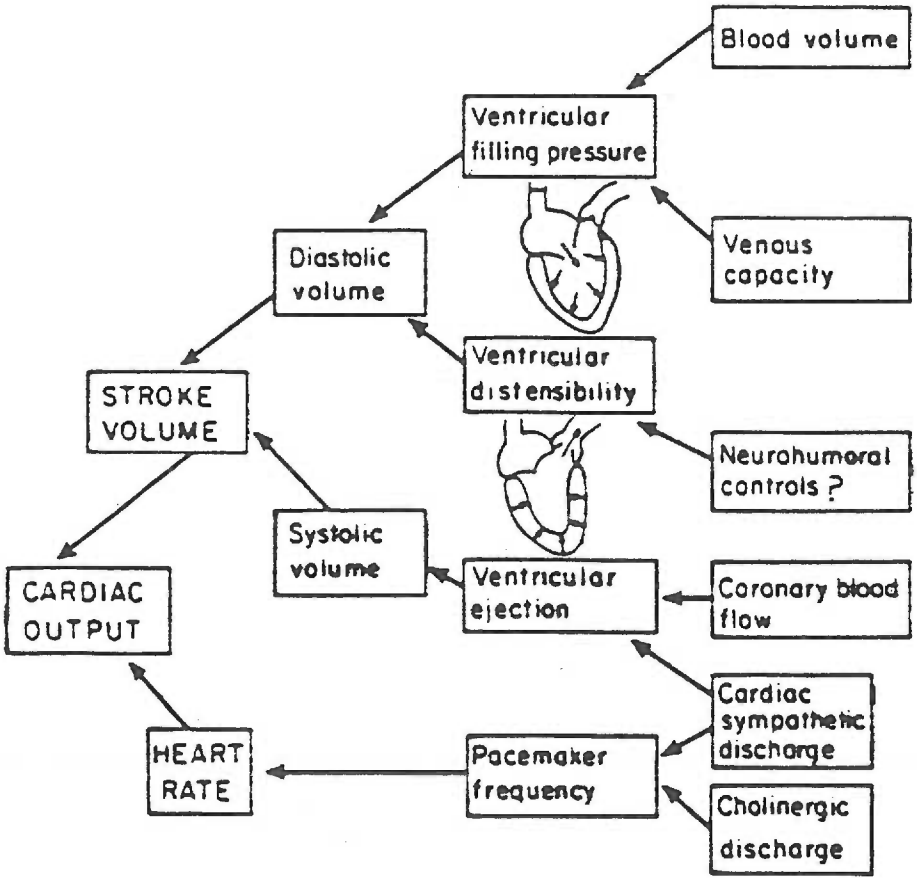


Figure 8. Factors determining cardiac output. The many interacting factors which determine the cardiac output present a wide variety of alternative mechanisms for control. Note that each branch point represents a potential site of control or compensation for any perturbation of the system. From Cardiovascular Dynamics (p. 177) by R. Rushmer, 1976, Philadelphia: W. B. Saunders. Copyright 1976 by W. B. Saunders Company. Adapted by permission.

further increase in preload will result in a decreased stroke volume (Frank-Starling Law of the Heart). Preload is affected by the blood volume, venous return, and distensibility (compliance) of the myocardium.

Afterload is affected by aortic valve and systemic resistance to flow. If the aortic valve, the outflow channel, is narrowed or the systemic arterial blood pressure is high, afterload increases. The heart must then develop increased contractility in order to eject blood from the heart during ventricular systole. Clinically, afterload is estimated using systemic vascular resistance.

Circulating catecholamines and sympathetic activation increase the contractile state of normally functioning myocardial cells. Clinically, changes in contractility can be estimated by determining if stroke volume increases or decreases, while preload and afterload remain unchanged. If stroke volume increases without a change in load, then contractility has increased and visa versa.

Synergy of contraction is negatively affected by areas of myocardium that are not functioning well. Infarcted, injured, or ischemic myocardium interrupts normal coordinated contraction of the myocardium. Asynchronous contraction decreases stroke volume.

Cardiac output, therefore, is affected by many interrelated mechanisms and is an important component of circulation. Arterial blood pressure is the product of cardiac output and systemic vascular resistance. Cardiac output, in turn, can be altered by changes in either pressure or resistance. An adequate cardiac output is necessary to maintain arterial blood pressure which in turn provides adequate systemic tissue perfusion.

Measurement of Heart Rate and Rhythm

To better understand the studies of rhythmicity of these variables, a discussion of how these variables are measured is included. Heart rate can be measured continuously by electrocardiographic monitors. Patients in ICUs are routinely monitored for electrocardiographic changes in heart rate and rhythm. Usually, the cardiac monitor is attached to the patient via cables and chest electrodes. The electrocardiographic signal is displayed visually on a monitor. Holter tape recorders can be used to record electrocardiographic leads for 24-72 hours. The tapes are analyzed at a later time to describe heart rate and rhythm over the recorded period.

Figure 9 illustrates the nomenclature for labeling the electrocardiogram using Leads II and V_1 are examples. When monitoring heart rhythm, electrodes are placed on the chest according to the lead selected. Figure 10 illustrates lead MCL_1 (modified left arm lead in the V_1 position), lead MCL_6 (modified left arm lead in the V_6 position, and M3 (modified lead III). Lead MCL_1 is commonly used to monitor heart rate and rhythm. Appendix B summarizes the electrocardiogaphic characteristics of each arrhythmia.

Measurement of Stroke Volume

Stroke volume can be measured directly during invasive cardiac catheterization. Alternatively, if cardiac output is measured, then stroke volume (ml/beat) can be derived by dividing cardiac output (ml/min) by heart rate (beats/min).

Measurement of Cardiac Output

Direct measurement of cardiac output requires surgical exposure

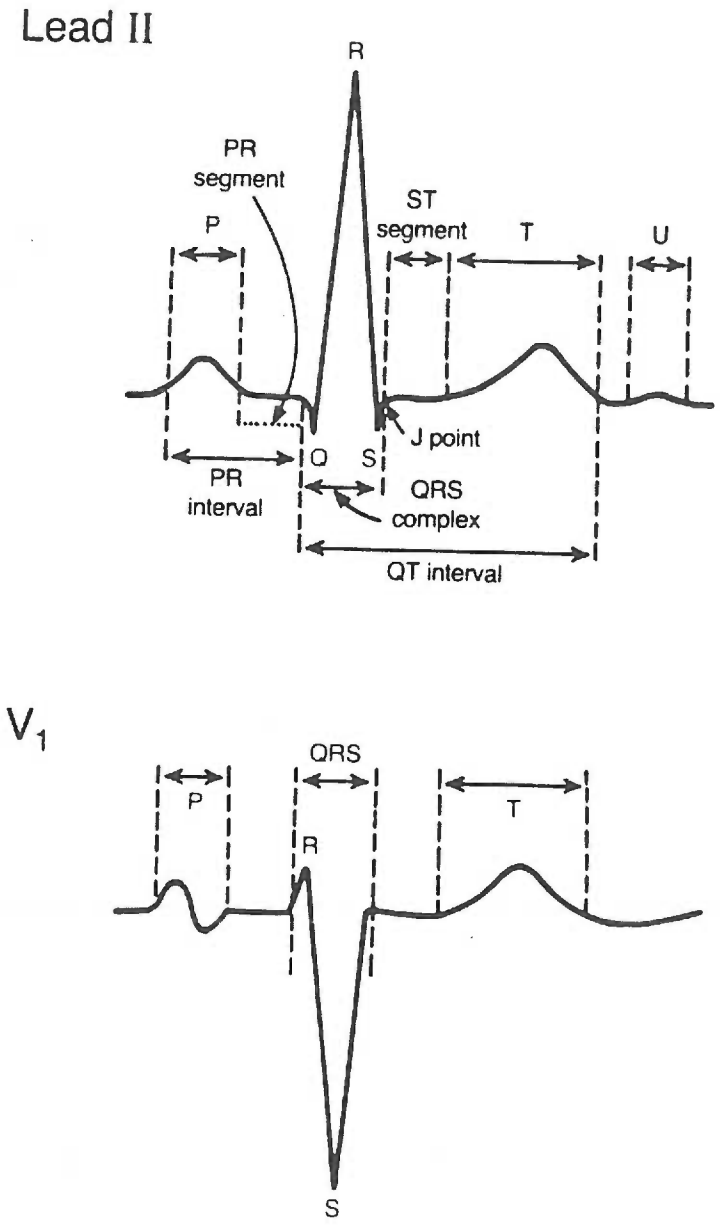


Figure 9. The normal electrocardiogram. Waves, complexes and intervals in Lead II and Lead V_1. From Cardiac Nursing (p. 312) by S. L. Underhill, S. L. Woods, E. Sivarajan Froelicher, and C. J. Halpenny, (Eds.) 1989, Philadelphia: J. B. Lippincott. Copyright 1989 by J. B. Lippincott. Reprinted by permission.

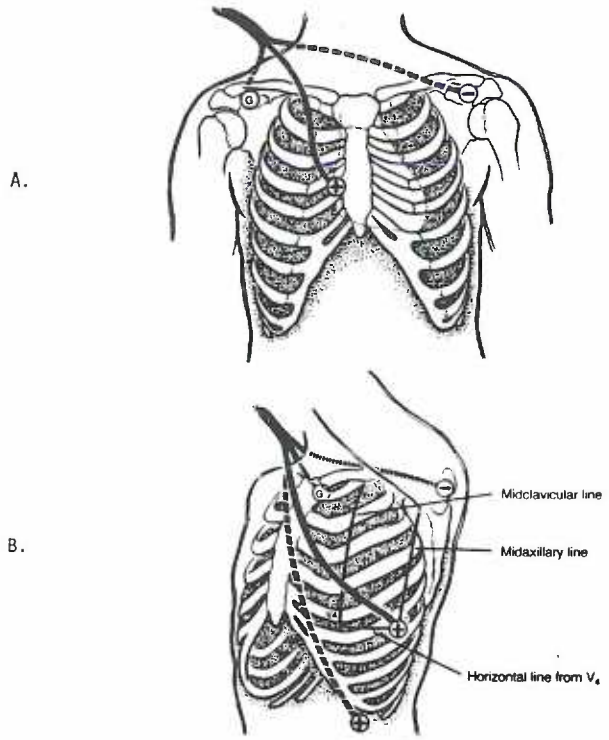


Figure 10. Common lead placement for cardiac monitoring. (A) Hookup for constant monitoring with MCL_1 (unbroken lines). The positive electrode is placed in the V_1 position; the negative electrode is placed on the outer one-fourth of the posterior left shoulder, and the ground is placed on the posterior right shoulder. (B) For MCL_6 the positive electrode is placed in the V_6 position. To obtain M3, the positive electrode is placed on the left upper abdomen (dashed line). From Cardiac Nursing (p. 498) by S. L. Underhill, S. L. Woods, E. S. Froelicher, and C. J. Halpenny, (Eds.) 1989, Philadelphia, J. B. Lippincott. Copyright 1989 by J. B. Lippincott. Reprinted by permission.

and cannulation of a central artery and vein. Measurements are made using flowmeters and are useful for animal studies (Guyton, 1986), but measurement of cardiac output in humans must be done by indirect methods.

Fick Method

The Fick principle states that the amount of a substance taken up or released by an organ is the product of its blood flow and the difference in the concentration of the substance between the organ's arterial and venous blood. Oxygen is a substance that can be readily measured. By rearranging the Fick equation, cardiac output (CO) can be computed as oxygen (O_2) consumption divided by the arteriovenous-oxygen (AVO_2) difference (Yang et al., 1988).

$$CO\ (l/min) = \frac{O_2\ \text{consumption (ml/min)}}{AVO_2\ \text{difference (vol \%)}\ X\ 10}$$

The measurement of oxygen consumption and arteriovenous oxygen difference must be performed while the subject is in a steady state. To measure oxygen consumption, the subject must breathe room air and exhale into a collection bag or monitor. The arteriovenous-oxygen difference is obtained by sampling the blood from an artery and a vein, then measuring and subtracting the arterial oxygen content from the venous oxygen content. This method of measuring cardiac output is the gold standard method in humans, but is complex and cannot be used in patients who are receiving oxygen or who are on mechanical ventilators (Loveys, 1986).

Dilution Method

In 1897, Stewart introduced the indicator dilution method of cardiac output measurement. Hamilton and associates extended this work and developed the Hamilton equation (Kinsman, Moore, & Hamilton,

1929; Hamilton, Moore, & Kinsman, 1932):

$$CO = \frac{I \times 60}{C_m \times t}$$

where CO is the cardiac output in l/min, I is the amount of indicator injected in mg, 60 is 60 sec/min, C_m is the mean indicator concentration in mg/l, and t is the total curve duration in sec. The indicators used include dye, temperature, and I^{131} (albumin). Dye-dilution and thermodilution are commonly used.

Dye-dilution method. A known volume of dye is injected rapidly into either the vena cava or right atrium, and the concentration of dye in the arterial blood is measured with a densitometer. Blood specimens are drawn at the time of injection through the first measurement of dye, the disappearance of dye, and until the dye recirculates. Measurements are plotted as dye concentration over time, with the area under the curve used to derive cardiac output (Guyton, Jones, & Coleman, 1973). Difficulties with this method include calibration of the equipment, instability of the dye which requires that it be prepared daily, need to withdraw well-mixed blood at a constant rate, requirement of both arterial and venous catheters, and recirculation of dye which limits frequency and accuracy of measurement (Guyton et al., 1973; Daily & Schroeder, 1989). In most clinical settings, the dye-dilution method compares well with the Fick method and is easier to perform.

Thermodilution method. The thermodilution method of measuring cardiac output was introduced by Fegler in 1954. This method uses a vascular thermal sensor with a thermal indicator as a method to obtain cardiac output using the basic indicator dilution method. A change in blood temperature from the right atrium to the pulmonary artery is

used as the indicator. A known quantity of cold fluid (at least 10°C less than the blood temperature) is injected into the right atrium via a pulmonary artery catheter (Ellis, Gold, Rees, & Lillehei, 1972). A thermistor at the distal tip of the catheter measures temperature in the pulmonary artery (Figure 11). Serial pulmonary artery temperature measurements are measured and plotted on a curve describing temperature change over time after injection of the cold solution (Figure 12). Cardiac output is derived using the formula shown in Figure 13 (Yang et al., 1988, p 59).

The thermodilution technique of cardiac output measurement has become a common technique used at the bedside of the critically ill (Forrester, Ganz, Diamond, McHugh, Chonette & Swan, 1972). A pulmonary artery catheter and cardiac output computer are necessary. In humans, cardiac output obtained using thermodilution technique has compared well with values obtained using the Fick method (Khalil, Wong, & Rapaport, 1965; Branthwaite & Bradley, 1968; Enghoff, Michaelsson, Pavek, & Sjogren, 1970; Vandermoten, Bernard, DeHemptinne, Gillet, & Lenaers, 1977; Zisserman et al., 1979; Van Grondelle, Ditchey, Groves, Wagner, & Reeves, 1983; Carpenter, Nair, & Straw, 1985) and dye-dilution method (Ganz, Denoso, Marcus, Forrester, & Swan, 1971; Weisel, Berger, & Hechtman, 1975; Saadjian, Quercy, & Torresani, 1976; Kohanna & Cunningham, 1977; Fisher et al., 1978). In animals, cardiac output obtained using the thermodilution technique has compared well with values obtained using the "gold standard," direct flow measurement (Sanmarco, Philips, Marquez, Hall, & Davila, 1971; Meisner, Hagl, Heimisch, Mayr, Mendler, Struck, Walther, & Sebening, 1974; Levine & Sirinek, 1981; Renner & Sakuma, 1989).

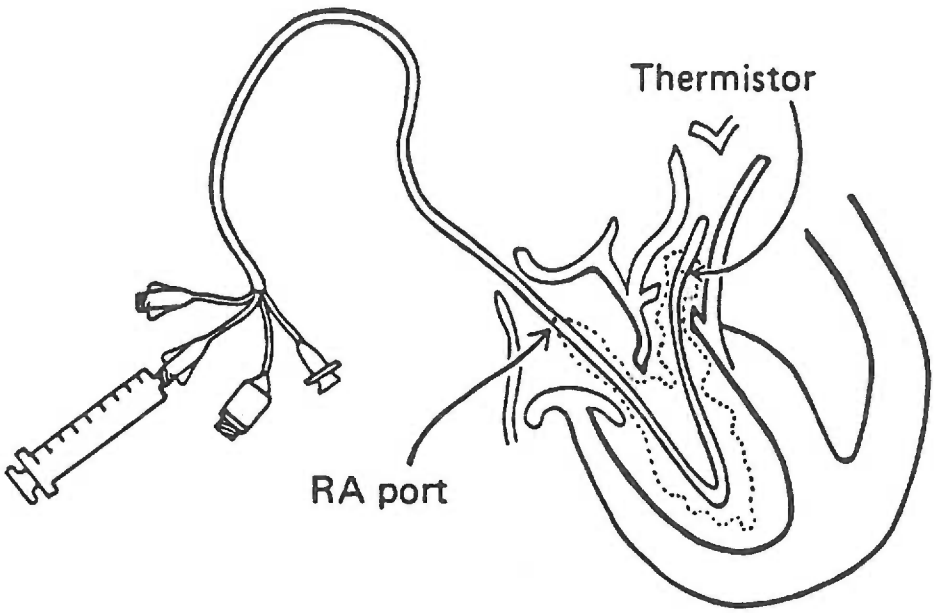


Figure 11. Injection into the right atrial port of a pulmonary artery catheter. From Cardiac Nursing (p. 464) by S. L. Underhill, S. L. Woods, E. Sivarajan Froelicher and C. J. Halpenny, (Eds.) 1989, Philadelphia: J. B. Lippincott. Copyright 1989 by J. B. Lippincott. Reprinted by permission.

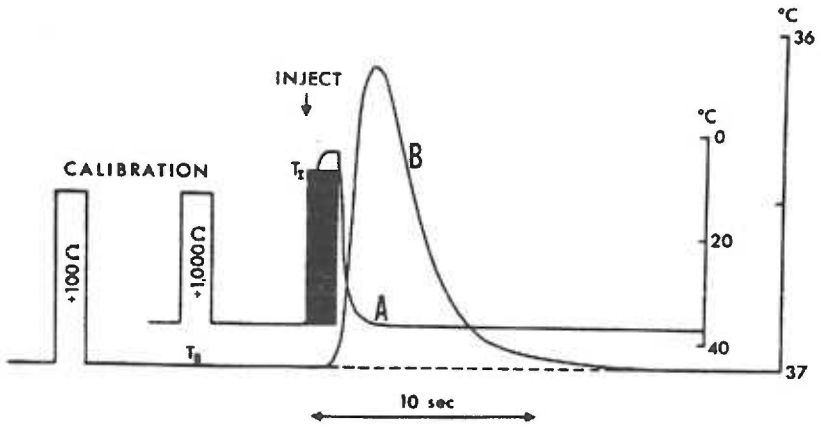


Figure 12. Diagrammatic representation of thermodilution curves for cardiac output. Curve A is recorded within the lumen of the catheter for determination of the mean injectate temperature (T_I). Curve B is the temperature recorded in the pulmonary artery. (T_B). From "Measurement of Blood Flow By Thermodilution" by W. Ganz and H. J. C. Swan, 1972, American Journal of Cardiology, 29, p. 241. Copyright 1972 by The American Journal of Cardiology. Reprinted by permission.

$$CO = \frac{V_i \rho_i C_i (T_b - T_i) \times 0.82 \times 60}{\rho_b C_b \times \int_0^\infty \Delta D_b(t)dt \times K}$$

where

V_i = Volume of injectate (ml)
ρ_i = Specific gravity of injectate
ρ_b = Specific gravity of blood
C_i = Specific heat of injectate
C_b = Specific heat of blood
T_b = Initial temperature of blood (°C)
T_i = Initial temperature of injectate (°C)
0.82 = Empirical correction factor for indicator loss between end and tip of the catheter
60 = 60 seconds/minute
K = Calibration factor for the curve (°C/mm deflection)

$\int_0^\infty \Delta D_b(t)dt$ = Area under the deflections-time curve registered following injection of the thermal indicator, in °C sec.

Figure 13. Formula to derive cardiac output by thermodilution (Yang et al., 1988, p. 59).

Periodicity of Selected Cardiovascular Variables

Temporal variation in cardiovascular physiological variables has been recognized since the second century in the writings of the Greek physician Galen, but, it was not until the 19th century that a 24 hour rhythm in selected cardiovascular variables was demonstrated. During the last 50 years, numerous studies have documented circadian, ultradian, and circannual rhythms in selected cardiovascular variables such as cardiac output, stroke volume, heart rate, arterial blood pressure, blood flow, capillary resistance, and blood and plasma volume (Smolensky et al., 1976b). Appendix C summarizes selected information about studies of the periodicity of heart rate and rhythm, stroke volume, and cardiac output.

Determinants of Stroke Volume

Data are available that describe the circadian periodicity of some of the determinants of stroke volume (preload, afterload, and contractility). No study could be found that described daily variation in preload. In humans, significant circadian rhythms have been found in blood volume which contributes to preload with acrophases (time of peak of fitted cosine curve) occurring 11-17.5 hours after midsleep (the middle of the sleep period)(Finlayson, Dagher, & Vandam, 1964; Morimoto, & Shiraki, 1970; Smolensky et al., 1976b).

There is much evidence that systemic blood pressure (a large component of afterload) has a circadian rhythm with the acrophase occurring 12-13 hours after midsleep (Smolensky et al., 1976b). In seven healthy humans, capillary resistance was found to have a large amplitude circadian rhythm with the acrophase approximately 5 hours

after midsleep (Doring & Riecke, 1952; Smolensky et al., 1976).

Wertheimer and coworkers studied urinary catecholamines and myocardial function using systolic time intervals in 10 hospitalized patients without cardiovascular disease. Myocardial contractility can be estimated using these intervals. They measured left ventricular ejection time (the duration of left ventricular ejection), QS_2I (total duration of left ventricular systole determined from the onset of ventricular depolarization to the closure of the aortic valve), and the pre-ejection period (the span beginning at ventricular depolarization until opening of the aortic valve) and found circadian rhythms in these parameters. The acrophase for urinary catecholamines and systolic time intervals were 12 hours apart with the former occurring just after the mid-activity period and the latter occurring during sleep. Catecholamines increase myocardial contractility and improve myocardial function, reducing the length of systolic time intervals. Thus, a difference of 12 hours was expected and was confirmed (Wertheimer, Hassen, & Delman, 1972; Wertheimer, Hassen, Delman, & Yaseen, 1974; Smolensky et al., 1976b).

Heart Rate

For the period prior to 1970, 14 studies of heart rate periodicity were found (Appendix C). In 12 of these studies the subjects were healthy normal men and women, while the other two studies included individuals with hypertension or cardiac disease. Subjects' ages ranged from early teens to the eighties. Analysis of data was generally graphic and descriptive in nature.

A circadian rhythm in heart rate was found even when subjects were kept at bedrest or in constant conditions (Schaefer, Clegg,

Carey, Dougherty, & Weybrew, 1967; Engel, Hildebrandt, & Voight, 1969). In day-active persons, heart rate peaked during the day, with the trough during the night usually during sleep. Heart rate was found to decrease progressively during sleep, with increased variability during rapid eye movement (REM) sleep that occurred later in the night (Snyder, Hobson, Morrison, & Goldfrank, 1964). Heart rate ranged anywhere from 3.6 beats per minute in one study to 27.3 beats/min in another study.

Heart rate was found to increase with meals, activity, and fever (Kleitman & Ramsaroop, 1948) and to decrease with inactivity, rest, and time of customary sleep (Kleitman & Kleitman, 1953). Heart rate and body temperature followed closely: for every $1^{\circ}F$ increase in temperature, heart rate increased 10-15 beats/min. Of historical interest, Guy (1839) found that the increase in heart rate associated with meals was greater and more lasting in the morning than in the evening.

Kleitman and Ramsaroop (1948) found circadian, weekly, monthly, and seasonal changes in heart rate in 10 healthy male and female subjects ranging from teenagers to middle-aged individuals. Heart rate was found to increase in the summer, May through September.

Kaneko, Zechman, & Smith (1968) used cosinor analysis in studying heart rate collected between 0900 and 2230 for 1-3 days in eight healthy subjects. They found periods of 25-27 hours, with acrophases between 1600 and 1900, and a half-amplitude (mesor to acrophase) of 11 beats/min.

For the next decade, 1970-1979, 48 studies of heart rate

periodicity were found (Appendix C). During this time, methods of data collection and analysis improved. Thirty of these studies included healthy male and female adults as either study subjects or as control subjects. Patient groups studied included individuals with the following diagnoses: cardiovascular disease, coronary heart disease, hypertension, myocardial infarction, toxic coma, breast cancer, leprosy, heart transplantation, complete heart block, premature ventricular beats, mitral valve prolapse, congestive heart failure, endogenous and neurotic depression, and quadriplegia. Other patients studied included those in surgical intensive care units. For these 48 studies, ages ranged from 18-81 years. Analysis procedures included graphic displays, descriptive statistics, t-tests, analysis of variance, non-parametric procedures, power spectral analysis, regression, correlation, complex demodulation, periodigrams, autocorrelograms, and cosinor analysis. Each of these procedures provides different information about the time-series data.

Circadian rhythms in heart rate were found in most subjects in most of these studies even when subjects were kept at bedrest (Halberg et al., 1970; Reinberg et al., 1970; Winget et al., 1972; Orr & Hoffman, 1974; Mann, Miller-Craig, Melville, Balasubramanian, & Raftery, 1979; Winget, DeRoshia, & Sandler, 1979) or in a controlled environment (Winget, Vernikos-Danellis, Deroshia, Cronin, Leach, Rambaut, 1974; Baust, Irmscher, Jorg, & Sommer, 1976). In most subjects, heart rate peaked during the day and decreased during the night. The difference in heart rate between the day and night ranged from 3.9-48 beats/min. Apfelbaum and coworkers found that changing meal times did not affect the acrophase or amplitude of the heart rate

in 36 obese but otherwise healthy, young females (Apfelbaum, Reinberg, & Lacatis, 1976). Miller and Helander (1979) found that heart rate decreased during the night in two day-active young, healthy males even when the subjects remained awake.

To determine whether there was a 90-100 minute period in heart rate, Wilson and colleagues studied 10 surgical intensive care unit patients and found no such period (Wilson, Kripke, McClure, & Greenburg, 1977). Unfortunately, no other time periods were examined. Kawasaki and coworkers found circadian and circatrigintan (30 $\pm$ 5 days) rhythms in heart rate in two healthy females (Kawasaki, Matsuoka, E. Halberg, & F. Halberg, 1978). One had 24-hour and 24-day periods; while the other had a 24-hour and 29-day periods. In three astronauts, periods of 21.5-24 hours and 90 minutes were found in heart rate (Rummel, 1974).

A circaseptan rhythm (7 days $\pm$ 3 days) in heart rate was found in a 37-year-old male who measured his heart rate once daily (time of measurement not stated) for one year (Malmstrom, 1973). Heart rate ranged from 52-84 beats/min. Peak heart rates occurred on Saturday and Monday with the trough on Sunday. A monthly (28-30 days) rhythm was found in heart rate data collected for three years in 8786 females aged 18-50 years (Freedman, Ramcharan, Hoag, & Goldfein, 1974). Non-contraceptive users (just over one-half of the subjects), had a mean age of 35.4 years. Their mean heart rates ranged from 69.5-71.5 beats/min over the menstrual cycle. The remaining patients, who used contraceptive drugs, had a mean age of 30.2 years. Their mean heart rates ranged from 68-73 beats/min with 90% from 71-72.5 beats/min. Data were analyzed using polynomials and cosines fitted by regression,

but were found by the authors to be not informative and were therefore not presented in the article. Using cosinor analysis of group heart rate data, Reinberg and coworkers found no heart rate circadian rhythms in 20 patients in deep coma following drug overdoses. Persons in deep coma may have alterations in their timekeeping system. Heart rate data were collected at 4-hour intervals, an interval that may have been too long to detect heart rate changes in these ill adults. Patients were in varying degrees of coma, and no individual data analyses were presented (Reinberg, Gervais, Pollak, Abulker, & Dupong, 1973).

Circadian and ultradian rhythms in heart rate were found in six patients with myocardial infarction in a coronary care unit (Kuzel, 1973). Cosinor analysis indicated that all had 24-hour rhythms and one to four patients had ultradian rhythms (16, 4.8, 8, 2.82, and 1.41 hours). Acrophases for the 24-hour rhythm varied from 0100-1525. Patients' sleep-wake cycles prior to admission were not known, and some of the acrophase times suggested that night-active persons may have been included in the sample. Half-amplitudes (mesor to acrophase) ranged from 4.9 ± 1.1 to 8.1 ± 1.1 beats/min.

For the time period 1980 to present, 97 studies were found that describe heart rate periodicity. In more than 60 of these studies, the subjects were normal, healthy men and women. Other studies included subjects with the following diagnoses: myocardial infarction, coronary heart disease, cardiovascular disease, arrhythmias, valvular heart disease, hypertension, congestive heart failure, postural hypotension, mitral valve prolapse, infection, cirrhosis, epilepsy, thyroid toxicosis, Cushing's syndrome, diabetes,

shock, drug overdose. Many of these studies were conducted with hospitalized patients, and several involved patients in ICUs. The age range was from 2 weeks to 100 years, although most were adults.

Data analysis in this group of studies was similar to that of the previous decade, with more researchers using cosinor analysis. In addition, some researchers used Hotelling's T^2 (multivariate analysis for vectoral units). As in the 1970 studies, heart rate was found to have a circadian rhythm in most subjects in most studies, even when subjects were kept at bedrest (Endo et al., 1981; Benoit, Foret, Merle, & Reinberg, 1981; Bernardi et al., 1987; and Cugini, Lucia, Letizia, Murano, & Scavo, 1987). In most subjects, heart rates peaked during the day and were lowest during the night.

When Ahnve and coworkers studied 12 young healthy male subjects who were kept awake for 64 hours in a constant conditions, the circadian rhythm of heart rate was largely obliterated (Ahnve, Theorell, Akerstedt, Froberg, & Halberg, 1981). E. Halberg and coworkers found not only a circadian heart rate rhythm, but also a 11.9 hour rhythm in a 60 year old female who was monitored for two 26-day periods (E. Halberg, F. Halberg, & Shankaraiah, 1981).

Circadian and circannual heart rate rhythms were found in a healthy, 45-year-old mother and her two daughters, ages 9 and 13 years who measured their pulses daily or several times daily for 3-5 years (times of measurement were not provided). The mother's acrophases for each year studied shifted from April through December; both daughters' acrophases occurred in July. Data on circadian rhythms were not reported (Halberg, Reinberg, & Lagoguey, 1983). DeScalzi and coworkers found circadian and ultradian rhythms in heart rate in

normal subjects (n=11) and in patients (n=5) with coronary heart disease (DeScalzi et al., 1984).

In 1984, Halberg and associates found ultradian (3.43 hours), circadian (24 hours), and circannual (1 year) rhythms in heart rate in 40 healthy male adults. Heart rate acrophase occurred at 1400 and early in April. The rhythm amplitude decreased with increasing age. In the 23-30 year age group the circadian half-amplitude was 12.44 beats/min; while in the 51-60 year age group was 9.42 beats/min (Halberg, Drayer, Cornelissen, & Weber, 1984). This reduction in amplitude with age is consistent with the findings of others (Tammaro, Casale, & Nicola, 1986; Cugini et al., 1987; and Sensi, Capan, Angelucci & Guagnamo, 1987). Circadian and ultradian (12, 8, and 6 hours) rhythms in heart rate were found in 36 untreated subjects with normal blood pressure or borderline hypertension (Bousquet, Chau, Poncelet, Warebourg, & Carre, 1988).

Domenichelli and coworkers found a circadian rhythm in heart rate in 39 patients with myocardial infarction. The acrophase was 1731 and the half-amplitude was 13.7 beats/min (Domenichelli et al., 1980). Aslanian and coworkers also found a circadian rhythm in heart rate in 141 patients with coronary heart disease who were studied on the second and third day of hospitalization. The acrophase was 1500 with a half-amplitude of 2.9 beats/min (Aslanian, Adamian, Grigorian, Bagdassarian, & Assatrian, 1980). Morrison and coworkers also found 24-hour rhythms in heart rate in 44 patients with myocardial infarction, before, during, and after hospitalization. No cosinor analysis was performed. Heart rate peaked between 1200 and 1800, and was lowest during the night (2400-0600)(Morrison, Kumar, Portal, &

Aber, 1981).

Gologorsky and coworkers found that heart rate circadian rhymicity was disordered in 79 surgical patients. For some postoperative patients, they found periods of 6-7 hours and 13 hours (Gologorsky, Grinenko, & Vereschagina, 1981).

Leach and coworkers studied a male patient who was in coma for 10 days following coronary bypass surgery. Circadian and infradian rhythms (4 and 7 days) in heart rate were found (Leach et al., 1983).

Mancia and coworkers found a circadian rhythm in heart rate in a study of 89 hospitalized patients. Peak heart rate occurred at 1230; lowest heart rates occurred from 2300-0430 (Mancia et al., 1986).

Farr and coworkers found a circadian rhythm in heart rate in 11 surgical patients postoperatively in the hospital and later at home. The acrophase shifted from 2200 in the hospital to 1300 at home. This finding may reflect differences in the rest/activity cycle between the two settings. Unfortunately, no data were obtained during sleep (Farr, Keene, Samson, & Michael, 1984).

Karjalainen and Viitasalo (1986) found that the amplitude of the circadian heart rate rhythm increased in 27 males with a febrile upper respiratory infection when compared to an afebrile recovery day. In 1986, Weber found in a large group of cardiac patients (N=1974) that circadian periodicity in heart rate was lost as left ventricular function worsened. Carpeggiani and coworkers found that of 11 male patients with variant angina in the coronary care unit for 4-13 days, 64% consistently maintained a circadian rhythm in heart rate. Peak heart rate occurred during the day (Carpeggiani et al., 1987).

Cugini and coworkers found a circadian rhythm in heart rate in 7

of 10 adult patients in shock in an emergency room. Acrophases were extremely variable. Three subjects had acrophases between midnight and 0500. It is unknown if these patients were day active individuals (Cugini et al., 1987). Felver and Hoeksel (1990) found circadian heart rate rhythm in seven of eight patients in a medical ICU. Ultradian rhythms (12, 6, and 4 hours) rhythms were also found in some patients.

Many studies have documented the rhythmicity of heart rate. In 1976, Smolensky and coworkers used cosinor analysis with 24 previous studies of heart rate periodicity fitting cosine curves of appropriate period (usually 24 hours) to the data. Table 2 summarizes the findings of these studies. Midsleep was used as the reference point for the acrophase (peak time of fitted cosine curve). When information on the sleep-activity schedule was not provided by the authors, but evidence indicated that the subjects were day active, sleep time was assumed to be 2300-0700, with midsleep at 0300. A circadian heart rate rhythm with a moderate half-amplitude of 2.5 to 8.5 beats/min was found in healthy subjects. The acrophases ranged from 9.75-18.75 hours after midsleep, with most approximately 13 hours after midsleep (Smolensky et al., 1976b).

In summary, circadian and ultradian rhythms in heart rate have been found in normal people and in ill adults with a large variety of diagnoses who were in and outside the hospital. Even though heart rate is affected by many exogenous factors, rhythmicity can still be detected in many of the groups studied. Only one study of postoperative cardiac surgery patients could be found and it was

Table 2

Circadian Rhythm of Human Heart Rate

No. and kind subs (no. days) [Δt, hrs]	P rhythm detection	Amplitude, A[b] (95% confidence limits)	Acrophase, φ[c] (95% confidence limits)	First author and year
1H(516)[~8]	<0.01	6.6(5.4 to 7.7)	1848 (1808 to 1928)	Halberg '69
5H(5)[4-8]	<0.01	8.5(3.1 to 13.8)	1400 (1228 to 1812)	Halberg '69
11H(1)[3]	<0.03	5.6%(4.6% to 6.5%)	1424 (1312 to 1540)	Zipp '74
7H(1)[4]	<0.002	7.7(4.5 to 10.9)	1256 (1048 to 1440)	Reinberg '74
1H(21)[2-10]	<0.01	9.3(7.2 to 11.4)	1436 (1332 to 1544)	Reinberg '74
10H(25)[1.5][d]	<0.01	2.7(1.7 to 3.7)	1344 (1040 to 1544)	Gunther '74
10H(25)[1.5][d]	<0.01	2.6(1.1 to 4.1)	1512 (1308 to 1732)	Gunther '74
10H(25)[1.5][d]	<0.01	2.5(0.7 to 4.3)	1500 (1300 to 1924)	Gunther '74
10H(25)[1.5][d]	<0.05	3.9(1.1 to 6.6)	1304 (1144 to 1828)	Gunther '74
13H(10)[1.5][d]	<0.001	7.5(2.9 to 12.1)	1240 (1116 to 1404)	Kanabrocki '73
12H(10)[1.5][d]	<0.001	6.4(0.4 to 12.4)	1400 (1308 to 1520)	Kanabrocki '73
35H(4-100)[1.5][d]	<0.001	3.5%(2.8% to 4.2%)	1120 (1036 to 1152)	LaSalle '74
11H(14-102)[~1.5][d]	<0.05	5.5(0.07 to 11.0)	1356 (1016 to 1648)	Halberg '67
1H(21)[1.5][d]	0.03	3.1(0.7 to 5.5)	0949 (0911 to 1027)	Sothern '74
1H(10)[1.5][d]	<0.01	5.4(2.8 to 7.0)	1537 (1343 to 1731)	Scheving '74
50H(16-64)[1.5][d]	<0.001	2.5(0.8 to 3.2)	1308 (1148 to 1440)	Halberg '74
6N(4)[4]	<0.005	5.0(3.0 to 7.0)	1324 (1156 to 0128)	Halberg '70
6E(4)[4]	<0.02	6.0(2.0 to 11.0)	1142 (0928 to 0120)	Halberg '70
7A(3-4)[1-10]	<0.009	8.0(3.0 to 14.0)	1300 (1108 to 1616)	Halberg '70
7D(1)[4]	<0.003	4.8(2.6 to 6.9)	1028 (0736 to 1328)	Reinberg '73
12D(14)[1.5][d]	<0.05	4.8%(0.6% to 9.0%)	1208 (0940 to 1600)	Levine '75
5I[e](2-3)[4]	<0.005	7.5%(3.4% to 11.7%)	1812 (1446 to 2138)	Reinberg '74
5I[f](2-3)[4]	<0.005	6.9%(2.6% to 11.3%)	1349 (1101 to 1637)	Reinberg '74
10L(10)[3][d]	0.05	4.8(0.2% to 9.5%)	1410 (0826 to 2056)	Enna '74

From "Circadian Rhythmic Aspect of Human Cardiovascular Function: A Review of Chronobiologic Statistical Methods by M. H. Smolensky, S. E. Tatar, S. A. Bergman et al., 1976, Chronobiologia, 3(4) p 341. Copyright, 1976 by Chronobiologia. Reprinted by permission. Subjects: H, healthy; A, astronauts in flight; N, healthy, bedrested without exercise or E, with isometric exercise; D, healthy but given special diet; I, adrenal insufficiency - cortisol given as two equal doses, between 0800 to 1300, and at 2000 (I^e) or in two unequal doses (I^i), 3/4 upon waking and 1/4 at bedtime; and L, leprosy

[a] Analysis by LSS and cosinor
[b] Amplitude (mesor to acrophase) in beats/min except when given relative to the mesor as a %
[c] Acrophase (φ) referenced to designated or estimated midsleep time and given as a delay in hours and minutes
[d] Data obtained during the waking hours only for designated length of study.

unknown if circadian rhythmicity of heart rate could be detected in that group of ill adults.

Heart Rhythm

Forty-nine studies that described the periodicity of selected cardiac arrhythmias could be found. These studies are summarized in Appendix C and are highlighted in Table 3. Most of these studies had normal subjects or patients with known arrhythmias. Other diagnoses were: hypertension, postural hypotension, acute myocardial infarction, mitral valve prolapse, coronary heart disease, and thyroid toxic disease. Data were generally analyzed using descriptive statistics, but some used cosinor analysis.

Most of the subjects in most of the studies had circadian rhythms in the incidence of premature ventricular contractions (PVCs), premature atrial contractions (PACs), paired PVCs, and ventricular tachycardia. Peak incidence or acrophase usually occurred while awake. Troughs usually occurred during sleep. Studies that have compared PVC frequency with stage of sleep have demonstrated inconsistent results. Some studies have shown that sleep stage is not related to frequency of PVCs (Monti et al., 1975; Broughton & Baron, 1978; Orr et al., 1979; Rosenberg et al., 1980; Otsuka et al., 1982b) Others have found increased PVC frequency during rapid eye movement (REM) sleep (Smith, Johnson, Rothfeld, Zir & Tharp, 1972; Pickering, Johnston, & Honour, 1978). Erickson (1987) found that PVCs decreased during REM sleep in a group of post myocardial infarction patients.

Others have found ultradian rhythms in the incidence of PVCs, PACs, and junctional escape beats (Kuzel, 1973; Orth-Gomer et al.,

Table 3

Periodicity of Heart Rhythms: Summary of Research Findings

Author/Year	Subjects/ Length of measurement	Arrhythmia	Period	Peak incidence	Trough incidence
Bristow et al. 1969	n=8 NLs; n=10 increased B/P; n=1 postural hypotension. 3 nights	Sinus bradycardia (n=19)		Sleep	None at 2300 before sleep
		PACs (n=1)		Sleep	None at 2300 before sleep
Sobotka et al. 1981	n=50 NLs 24 hr	PVCs (n=27)		n=4 sleep n=21 while awake n=2 sleep=awake	
		Sinus arrhythmia and Sinus bradycardia n=50		Sleep	
Smith et al. 1972	n=18 patients with arrhythmia in CCU 1 night	PVCs (n=17)		n=6 awake n=6 REM n=5 non-REM	
		2 or more PVCs in a row (n=11)		awake=sleep	
		PACs (n=10)		n=4 awake n=3 REM n=2 non REM n=1 awake=non REM	
		2 or more PACs in a row (n=7)		awake=sleep	
Kuzel 1973	N=6 MI patients 1 day	PACs	24 hr 12 hr (n=4); 3.4 hr (n=1); 0.06-1.6 hr (n=5)	Acrophase (group) 0902	
		PVCs	24 hr (n=3) 12 hr (n=1) 8 hr (n=2) 4.8 hr (n=2) 5.3 hr (n=1) 4 hr (n=1) .6-1.5 (n=2)	Acrophases 0743-1820	
		Junctional escape beats	24 hr (n=4) 16 hr (n=1) 12 hr (n=3) 8 hr (n=2) 3.4 (n=1) .5-2.7 (n=2)	Acrophases 0550-1621	
Hockenberger et al. 1974	N=10 MI patients 4 days	PVCs - day 1 PVCs - day 2 PVCs - day 3 PVCs - day 4		1200-2400 1200-1800 0600-1200 no specific time	
Winkle et al. 1975	N=24 MVP 24 hr	PVCs (n=18)		Awake	Sleep
		PACs (n=15)		Awake	Sleep
Kennedy et al. 1976	N=25 NLs with PVCs 24 hr	PVCs (N=25)		Awake (n=74%)	Sleep
		Couplets		Awake	Sleep
		Multifocal PVCs		Sleep (n=26%)	Awake
Clark et al. 1976	N=86 NLs 48 hr	Bradycardia and Tachycardias		Awake=sleep	

table continues

Table 3 (continued)

Author/Year	Subjects/ Length of measurement	Arrhythmia	Period	Peak incidence	Trough incidence
Brodsky et al. 1977	N=50 NLs 24 hr	Sinus bradycardia (n=12%)		Sleep	
		Sinus arrhythmia (n=50%)		Sleep	
		Sinus pause (n=68%)		Sleep	
		2° AV block - Type I (n=6%)		Sleep	
		PACs (n=56%)		Not stated	
		PVCs (n=50%)		Sleep n=8 Awake n=16 Equal n=1	
		VT (n=1)		Sleep	
Pickering et al. 1977	N=31 NLs and cardiac patients 24 hr	PVCs		Night (n=1)	Disappeared at night (n=8) Reduced number at night (n=22)
Steinbach et al. 1978	N=29 patients 24 hr	PVCs 24 hr (n=77%)		Day	Night
Kennedy et al. 1978	N=67 cardiac patients N=23 NLs 48 hr	PVCs		Mild to moderate exercise (n=50-80%) Sleep (n=8-26% patients)	
Morganroth et al. 1978	N=15 cardiac patients with PVCs 3-24 hr	PVCs			2400-0800
Pickering et al. 1978	N=12 patients with PVCs 24 hr	PVCs		Activity period and sleep onset n=2 REM n=1 Stage 3 & 4	Sleep 69.2% decrease in PVCs
		Paired PVCs and Multifocal PVCs		Wakefulness	
Michelson et al. 1980	N=20 cardiac patients with PVCs 24 hr X 4	PVCs Complex ventricular arrhythmias			Sleep (2400-0800) 20% decrease
Sensi et al. 1980	N=13 cardiac patients 24 hr	PVCs	24 hr	Acrophase 1534	
Domenichelli et al. 1980	N=39 patients with MI	PVCs CHB (n=2)	24 hr	Acrophase 1524 Atrial rate acrophase 1140 Ventricular rate acrophase 1227	
Tartini et al. 1980	N=52 MVP 24 hr	PVCs	24 hr	During activity	
Leach et al. 1981	N=20 cardiac patients 24 hr	PVCs	24hr (n=9)	Acrophase 1744	
Morrison et al. 1981	N=44 MI 24 hr X 3	PVCs Complex PVCs			Sleep Sleep

table continues

Table 3 (continued)

Author/Year	Subjects/ Length of measurement	Arrhythmia	Period	Peak incidence	Trough incidence
Andresen et al. 1982	N=42 patients with PVCs 24 hr X 3	PVCs Couplets (n=16)		Day=night (n=21) Day (n=14) Day (n=6)	Night (n=7) Night (n=2)
Orth-Gomer et al. 1982	1 n=42 CHD 2 n=32 NLS with CHD risk factors 3 n=29 NLs 24 hr	PVCs	All - 24 hr NLs - 6, 3.43 hr	Acrophase 1 - 1244 2 - 1220 3 - 1236	
Yanaga et al. 1982	N=16 with PVCs 24-72 hr	PVCs		n=2 night n=4 day n=10 same day and night	
Steinbach et al. 1982	N=87 patients with PVCs 24-96 hr	PVCs	24 hr in n=4	0700-2400	0000-0200
Leach et al. 1983	N=1 patient with CHD in coma after bypass surgery	PVCs Runs of PVCs	4.75 days; 7 days 24 hr; 3.9 days; 7 days		
Montague et al. 1983	N=45 with >100 PVC/day 24 hr	PVCs		n=17 with sleep	n=25 sleep
Rosenberg et al. 1983	n=50 NLs; n=50 with increased PVCs with sleep 24 hr	PVCs	24 hr patients only	NLs - awake Patients with sleep	
Canada et al. 1983	N=164 (n-124 cardiac patients; n=40 NLs) 24 hr X 3	PVCs	24 hr	1200-1600	0100-0500
DeSalzi et al. 1984	N=16 patients having PACs and PVCs 96 hr	PACs PVCs	24 hr n=8 24 hr (most) 5.25 to 17 hr n=8	Acrophases 0424-1812	
Saito et al. 1984	N=21 with VT 24 hr	VT	24 hr	0700-0900 and 1500-2100 n=18 had VT day > night n=3 had VT night > day	0100-0700
Dickinson et al. 1984	N=100 NLs 48 hr	PVCs		Day	Sleep
DeLeonardis et al. 1985	N=49 (n=21 NLs; n=28 risk for CHD) 4 days	PACs PVCs	24 hr; 4 hr, 12 min to 20 hr 24 hr; 5 hr 12 min to 17 hr	Acrophase 0424-1912 Acrophase 0900-2352	
Rasmussen et al. 1985	N=111 NLs 24 hr	PVCs	24 hr	1000-2000 increase with age	Night

table continues

Table 3 (continued)

Author/Year	Subjects/ Length of measurement	Arrhythmia	Period	Peak incidence	Trough incidence
Grosgogeat et al. 1986	N=134 NLs 24 hr	Supraventricular Extrasystoles PVCs		68% day 50% night 42% day 23% night	
Cafiero et al. 1986	N=34 (n=17 cardiac patients; n=17 NLs) 24 hr	PVCs	24 hr n=11 patients and n=13 NLs	Acrophases 1500-1800	
Lanza et al. 1986	N=7 patients with ventricular parasystole 24 hr	Parasystole	24 hr	Acrophase 1342	
Tammaro et al. 1986	n=30 aged NLs n=42 NLs young n=29 aged with CHD 24 hr	PVCs	24 hr in 43.3% NLs and 58.6% patients	NLs - 0600 CHD - Acrophase 1404 31.19% of those with CHD and 36.7% NLs had nocturnal acrophases	
Northcote et al. 1986	N=10 thyrotoxic 24 hr X 2	PACs PVCs VTs n=2		Middle 1/3 day for PACs and PVCs 0530-2100 0500-0830	 Sleep
Rossi et al. 1986	N=18 elderly 24 hr	PACs PVCs	24 hr n=9 24 hr n=5 (out of n=15)	Acrophases 0060-2152 Acrophases 0080-2300	
Orth-Gomer et al. 1986	N=147 NLs 24 hr	PVCs	24 hr	1100-1330	Sleep
Mir 1986	N=28 patients with arrhythmias 1 week	VT PVCs SVT		1200-2400 2000-2400 1200-2000	0400-0800 0000-0800
Muller et al. 1987	N=2203 deaths outside hospital due to MI (n=685 - CHD and arrhythmia deaths) 1 year	Death	24 hr	10-11 AM 5-6 PM	Night
Willich et al. 1987	N=429 SCD 38 years	Death	24 hr	7AM - 9 AM	9AM - 1 PM
Rebuzzi et al. 1987	N=406 patients in hospital 24 hr	PVCs VT n=32	 24 hr	 Acrophase 1102	
Biffi et al. 1987	N=10 with PVCs 24 hr	PVCs	24 hr (n=7)	Acrophase day	
Irwin et al. 1988	N=52 with PSVT	PSVT	24 hr	1600	

table continues

Table 3 (continued)

Author/Year	Subjects/ Length of measurement	Arrhythmia	Period	Peak incidence	Trough incidence
Kocovic et al. 1988	N=198 CHD & PVCs 24 hr	PVCs Pairs of PVCs VT	24 hr 24 hr 24 hr	1000-1500 1000-2300 0700-1200	0400 0100-0400 0100-0500
Lucente et al. 1988	N=94 with acute MI and VT 24 hr	VT	24 hr	Acrophase 1429	
Raeder et al. 1988	N=45 patients with PVCs 24 hr X 2	PVCs	24 hr	1000-1200	0500

NLs, normals; MI, myocardial infarction; PACs, premature atrial contractions; PVCs, premature ventricular contractions; MVP, mitral valve prolapse; AV, atrioventricular; REM, rapid eye movement; CHB, complete heart block; VT, ventricular tachycardia; PSVT, paroxysmal supraventricular tachycardia; and SCD, sudden cardiac death.

1982; DeScalzi et al., 1983; Leach et al., 1983; DeLeonardis et al., 1985).

Cardiac Output and Stroke Volume

Ten studies could be found that examined the temporal pattern of stroke volume and cardiac output. Tatsumi (1967) measured cardiac output indexed to BSA by a dilution method using I^{131} albumin in 44 patients with cardiac disease. Cardiac output was measured at 1500 and 2200, and subjects slept from 1500-2000. Cardiac index was consistently higher at 1500 than at 2200. Stroke volume was also indexed to BSA. When subjects were regrouped according to four grades identified by New York Heart Association, stroke index either remained unchanged or was lower at 2200 in all. This decrease in cardiac index at 2200 may have been due to sleep, inactivity, recumbency, or a circadian effect.

In 1967, Khatri and Freis measured cardiac output (dye-dilution method) and stroke volume at 2300 (awake) and during various stages of sleep in 15 healthy subjects. Peak cardiac output was 7.639 $\pm$ 1.248 l/min while awake and decreased during sleep to 6.702 $\pm$ 1.27 l/min. Stroke volume followed a similar pattern, with values of 117.6 $\pm$ 18.1 ml/beat during wakefulness and 108.1 ml/beat during sleep.

Bristow and coworkers (1969) measured cardiac output (dye dilution method) and stroke volume three times per night for three consecutive nights in 8 normal subjects, 10 hypertensives, and 1 subject with postural hypotension. Time of measurements relative to activity was unknown. Cardiac output showed no consistent change in normal subjects. In the hypertensive subjects, cardiac output decreased 6.2 $\pm$ 13.6% during sleep. Generally, cardiac output was

higher before sleep. Stroke volume increased a mean of 11.2 ml/beat during sleep in normals only (Bristow, Honour, Pickering, & Sleight, 1969). Measurement of the stroke volume may have been made during rapid eye movement sleep, resulting in an increased stroke volume. Also, this increase in stroke volume may have been due to the subjects horizontal position in bed, which would increase venous return to the heart and therefore preload.

Appelhoff and associates measured mean aortic blood velocity (an index of cardiac output) and stroke volume every 2-3 hours for 72 hours in four healthy men, aged 20-28 years. Velocity was measured by transcutaneous aortovelography. They found a circadian rhythm with a 9% decrease in cardiac output and a 15% decrease in stroke volume at night. Meals and activity increased cardiac output and stroke volume. Unfortunately, there was no cosinor analysis (Appelhoff, Fentrop, Hartung, Light, & Stelling, 1979).

In 1979, Miller and Helander measured cardiac output and stroke volume (by impedance plethysmography) in two day-active healthy males aged 33 and 34 years. Measurements were hourly for 48 hours in a laboratory setting. Subject 1 stayed awake during first night and slept the second night; Subject 2 slept the first night and stayed awake the second night. Cosinor analysis of the data for the awake 24 hours revealed a circadian rhythm in cardiac output and stroke volume with acrophases for cardiac output 2012 and 2254 and for stroke volume 0430 and 0048. Half-amplitudes for the cardiac output rhythm were 0.37 and 0.54 liters/min and for stroke volume were 3.9 and 9.3 ml/beat. Cardiac output decreased during sleep and during the night even when persons did not sleep. Cardiac output increased 1-2 hours

after meals due to increase in stroke volume.

In 1981, Ahnve and coworkers measured stroke volume by ballistocardiography (IJ amplitude) every three hours for 64 hours in 12 healthy men aged 19-30 years. The IJ amplitude corresponds to left ventricular contractility which is only one component of stroke volume. Subjects were isolated from external time cues in a constant environment. A significant circadian rhythm ($p=0.006$) was found with acrophase occurring at 2108 (Ahnve, Theorell, Akerstedt, Froberg, & Halberg, 1981).

In 1983, Halberg and coworkers reported that a circadian rhythm in cardiac output and stroke volume was found in a day-active person. The acrophase for cardiac output was 1445 and for stroke volume was 1430. No methods were given (Halberg et al., 1983).

Moskin (1984) measured cardiac output by Broemser-Ranke formula and sphygmograms of carotid and femoral arteries every four hours during the day (0700-2300) for three to six days in the winter and twice in the autumn in 10 polar scientists. Cardiac output maintained a 24-hour period independent of the light-dark cycle. Cardiac output peaked at 1500 (all three times) and was lowest at 0700 (all three times). The range was from 4.5-7.5 l/min. There was no cosinor analysis.

Adamian and coworkers (1984) measured cardiac output and stroke volume (using radiocardiography and the Starr formula) in 141 patients with coronary heart disease and in 26 healthy adults who were hospitalized. Significant circadian rhythms were found. Acrophases for cardiac output were as follows: 1309-1632 (patients) and 1930 (normals). Acrophases for stroke volume were 1252-1345 (patients) and

0325 (normals). Half-amplitudes for cardiac output were 0.26-0.31 l/min (patients) and 0.33 l/min (normals). Half-amplitudes of stroke volume were 2.6-3.2 ml/beat (patients) and 1.6 ml/beat (normals). Subjects may have included both day-and night-active persons. Customary entrainment was not discussed.

Smolensky and co-workers (1976b) analyzed three studies of stroke volume and five studies of cardiac output using cosinor analysis. In normal subjects they found circadian rhythms of moderate half-amplitude, varying 5%-23% from the stroke volume mesor and 7%-33% from the cardiac output mesor (Table 4). The acrophase for stroke volume ranged from 7.2-11.4 hours after midsleep. The acrophase for cardiac output ranged from 9.1-15.3 hours after midsleep (Kroetz, 1940; Kaiser & Maurath, 1949; Schroder et al., 1969). For cardiac output, one heart patient showed an acrophase of 17 hours after midsleep (Kroetz, 1940).

In general, stroke volume and cardiac output have been shown to have a circadian rhythm in healthy subjects with peaks during the day and lows during the night (even when subject stayed awake). Some studies have shown that stroke volume increases during sleep, while others have shown decreases with sleep. These differences may be due in part to the time of measurement related to the different phases of the sleep cycle. Cardiac output rhythm ranged from 0.26-2 l/min; the stroke volume rhythm ranged from 2.6-11.2 ml/beat.

The studies cited small numbers of subjects, used a variety of methods, and accounted for few variables. No study could be found that described the temporal pattern in cardiac output and stroke volume over one to two days in hospitalized adults in either general

Table 4

Circadian Rhythm of Stroke Volume and Cardiac Output

No. and kind subs (no. obs.)[Δ t, hrs]	Mesor, M M ± SE	Amplitude, A[a] (95% confidence limits)	Acrophase, Φ[b] (95% confidence limits)	First author and year
stroke volume (ml)				
1H(13)[2]**	127.4 ± 1.6	6.3 (4.2 to 8.5)	1124 (0852 to 1400)	Schroder '69
1H(17)[2]*	81.0 ± 3.6	18.4 (12.9 to 28.4)	1038 (0828 to 1232)	Kaiser '49
1H(17)[2]*	62.4 ± 1.6	8.6 (4.0 to 13.2)	0712 (0512 to 0916)	Kaiser '49
cardiac output (L/min)				
1H(17)[1.5]***	4.53 ± 0.03	0.30 (0.22to 0.38)	1520 (1416 to 1624)	Kroetz '40
1H(17)[1.5]***	4.25 ± 0.06	0.54 (0.36to 0.68)	1436 (1324 to 1544)	Kroetz '40
1H(13)[2]**	4.57 ± 0.23	1.52 (0.86to 2.18)	1056 (0920 to 1232)	Kaiser '49
1H(13)[2]*	3.53 ± 0.13	0.52 (0.16to 0.88)	0908 (0636 to 1144)	Kaiser '49
1P(12)[2]***	4.12 ± 0.03	0.27 (0.23to 0.31)	1704 (1636 to 1740)	Kroetz '40

From "Circadian rhythmic aspect of human cardiovascular function: A review of chronobiologic statistical methods" by M.H. Smolensky, S.E. Tatar, S.A. Bergman, et al., 1976, Chronobiologia, 3(4) p 349. Copyright, 1976 by Chronobiologia. Reprinted by permission. Subjects: H, healthy; P, heart patient.

[a] amplitude (mesor to acrophase)

[b] acrophase, Φ referenced to the estimated midsleep time and given as a delay in hrs and min.

* $0.01<p<0.05$; ** $0.001<p<0.01$; *** $p<0.001$.

or intensive care settings. It is unknown if rhythms with these amplitudes can be detected in physiologically unstable patients in intensive care units. There may be too much biological noise (effects of illness and treatment) masking detection. No study could be found that described the temporal pattern of simultaneously measured heart rate and rhythm, stroke volume, and cardiac output in critically ill adults in an ICU.

The Critically Ill Adult in the Intensive Care Unit

The critically ill hospitalized adult is usually placed in a highly-equipped ICU, in order to obtain around-the-clock care by specialized personnel. Most of these units have high nurse-to-patient ratios, for example one or more nurses assigned to one patient or one nurse to two patients. Staffing depends on patient acuity; many patients require constant care.

The patient may be attached to numerous devices that confine the patient to bed and may produce sound. Some of these devices are cardiac monitor leads with sensitive alarm systems; intravenous infusions in arms, neck, chest, or groin; oxygen tubing; urinary catheter and other drainage tubing; endotracheal tube and ventilator with sensitive alarms; and indwelling arterial, venous, and pulmonary artery catheters. The patient is commonly supine with the head of bed elevated 10 degrees or less (Woods, Grose, & Laurent-Bopp, 1982) and fears turning (Shovelton, 1979).

In order to provide care, the patient is disturbed frequently for observation, ordered medical therapies, and nursing interventions (DeMeyer, 1967; Dlin, Rosen, Dickstein, Lyons, & Fisher, 1971; Lindemuth, Breu, & Malooley, 1980). The room may be illuminated

constantly and the environment is often noisy (De Meyer, 1967; Woods & Falk, 1974; Bentley, Murphy, & Dudley, 1977; Orr & Stahl, 1977; Redding, Hargest, & Minsky, 1977; Lindenmuth et al., 1980; Ballard 1981; Hilton, 1985). There may or may not be windows, clocks, or calendars that the patient can see. Sounds that the patient can hear may include phones ringing, radio and television, talking of personnel, equipment noises and alarms (ventilators, suction, nebulizers, cardiac monitors, cooling blankets), treatment sounds (coughing and deep breathing, chest percussion, suctioning), ice machine, running water, flushing toilets, call lights and intercoms, and sounds of other nearby patients.

The intensive care environment is unfamiliar, disruptive, inconsistent, and stressful to most patients (DeMeyer, 1967). The pace of the ICU is very rapid, and patients are attended to quickly. Patients are moved in and out of the unit at all hours of the day and night, depending on which patients need the intensive care the most. Many patients cannot rest, let alone sleep, in this unstable, constantly illuminated, noisy environment. Sleep deprivation and sensory overload are common occurrences (Dlin et al., 1971; Wilson, 1972; Orr & Stahl, 1977; Ballard, 1986). Many patients feel exposed, dependent, alone, afraid, anxious, uncomfortable, and annoyed (Shovelton, 1979; Lindenmuth et al., 1980; Ballard, 1981). Some patients withdraw, while others become hyperalert (Dlin et al., 1971).

The internal environment of the critically ill patient is also constantly changing in response to illness and therapy. For example, patients usually receive multiple intravenous infusions, such as

vasodilators, inotropes, parenteral nutrition, blood, albumin, maintenance fluid and electrolytes, and many intravenous medications. In addition, patients usually receive intensive respiratory therapy such as suctioning, vibration, and aerosol treatments. Other examples of treatments that could affect the patient's internal environment include wound care; insertion, maintenance, and removal of intravenous lines, nasogastric tube, endotracheal tube, chest tubes, or other drainage tubes; and body position change. Activities of daily living (such as bathing, eating, toileting) in the ICU are disturbed and are usually performed differently from usual and may cause the patient concern or anxiety. As a result of this ICU experience, patients might be expected to have wide fluctuations in measured physiological variables.

Whether all patients in ICUs have circadian rhythms in heart rate and rhythm, stroke volume, and cardiac output is unknown. The overt rhythm may be so affected by exogenous influences that an underlying endogenous rhythm may not be detectable, even if it persists.

Summary

No published studies could be found that described circadian and ultradian variations in the simultaneously measured cardiovascular variables of heart rate and rhythm, stroke volume, and cardiac output in critically ill adults in an ICU. If circadian and ultradian variations in these variables can be identified, characterization of their nature would be useful. Knowing the fluctuations of these variables in these patients would be useful in defining the limits of the range in relation to time of day, as illustrated in Figure 14.

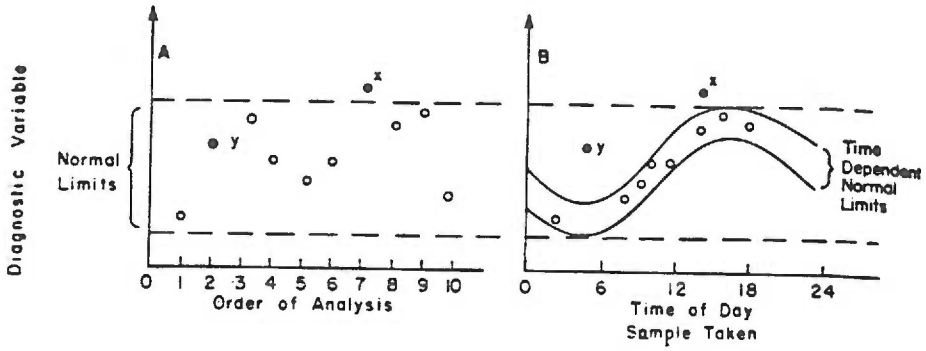


Figure 14. Normal limits of a variable. Normal limits for a diagnostically useful variable plotted (A) without and (B) with regard to the time of day. When the time of day is taken into account, the detection of abnormal values is improved, so that not only value x but also value y can be identified as being outside the ormal range. From The Clocks That Time Us (p. 346) by M. C. Moore-Ede, F. M. Sulzman, and C. A. Fuller, 1982, Cambridge, Massachusetts: Harvard University Press. Copyright 1982 by the President and Fellows of Harvard College. Reprinted by Permission.

Nursing therapies could also be timed more appropriately if the daily fluctuations in these variables were known. Periods of resistance and susceptibility to insult could be identified. For example, if arrhythmias occurred with increased frequency at a specific time, then interventions could be timed to prevent, detect, or eliminate the arrhythmia. During periods of no or decreased arrhythmias, interventions that increase myocardial oxygen demand could be planned (e.g. meals, procedure, visiting, activity, etc.). Knowledge of baseline fluctuation is also useful in planning research that involves cardiovascular or other physiological variables in these patients. In research, baseline change must be accounted for and controlled when possible. Nursing research that would determine the effect of altering the external environment (lights, noise, meals, social cues, etc.) on the daily rhythmicity of these variables would be useful.

Purpose of the Study

The purpose of this study was to describe the temporal pattern in heart rate and rhythm, stroke volume, and cardiac output over 24-48 hours in critically ill adults in a cardiac surgical ICU.

CHAPTER III

METHODS

This chapter presents the design of the study, sample and setting, instruments, data collection procedures, and information related to the use of human subjects. The chapter concludes with a description of the data analysis procedures.

Design

A descriptive, time-series design was used to characterize the temporal pattern of heart rate and rhythm, stroke volume, and cardiac output for 24-48 hours in critically ill adults in a cardiac surgical ICU. A time-series design can be used to characterize patterns over time, to analyze unique fluctuations of a variable through time, and to provide a framework for predicting further changes in the variable for the individual (Woods & Catanzaro, 1988). A study time of 24-48 hours was selected to allow for one complete circadian cycle and possibly two in the same individual and also because of the practical limitation that intravascular lines needed for measurement are usually in place for two days. When two cycles could be measured, individual description could be improved and internal validity increased.

Sample and Setting

A convenience sample of six subjects was selected from the patients in a eight-bed cardiac surgical ICU of a large Portland hospital. Sample, although small, was adequate to determine if circadian rhythms could be detected in this type of patient. Male and female patients who were between the ages of 18-70 years, and were to have a thermodilution pulmonary artery catheter and a bladder temperature probe in place were screened preoperatively for inclusion

in the study. The bladder catheter was necessary to provide data for a concurrent study of temporal patterns in body temperature in the same sample.

Exclusion criteria included: (a) atrial fibrillation since derivation of stroke volume is dependent on a regular heart rhythm; (b) neck injuries that involved the brain stem, since normal brain stem function was necessary for central regulation of cardiac function; (c) contraindications to cardiac output measurement at least every 4 hours, since 15-25 ml of intravenous solution is required for each measurement and patients with fluid excess may not be able to tolerate this additional volume; (d) predicted placement of either the pulmonary artery catheter or bladder temperature probe for less than 24 hours; (e) being in the ICU more than one week, since physiological rhythms could be adjusting to the new environment; and (f) expected stay in the ICU of less than 24 hours.

Instruments

Data Collection Forms

Data collection forms included a Background Variable Form (Appendix D), Status Record (Appendix E), Debriefing Log (Appendix F), and three data collection records (Appendix G). The Background Variable Form contained general demographic information about the subject, height, weight, sensory deficits and therapeutic aids, summary of medical history, current diagnoses, surgery information, medications, level of consciousness, customary prehospital daily pattern and time of day preference, and hospital acuity score. The Status Record was completed at change of shift and contained information about the patient's environment, including air

temperature, light intensity, mechanical tactile stimuli, time cues, fluid and nutrient infusions, and oxygen therapy. The Debriefing Log was completed at the end of every shift and listed problems, suggestions, successes, and other comments.

The three data collection forms were used to record the following data: date, time, heart rate and rhythm, five temperatures (bladder, rectal, pulmonary artery, oral, and air), cardiac output, urine output, ventilator settings, fluid and nutrients, devices and bed covers, medications, oxygen, body position, self-initiated movement, self-verbalization, time cues, light intensity, sleep-wake status, Glasgow coma scale score, miscellaneous laboratory values, and events in the room.

Watches

The investigators' watches were synchronized at every shift change to the wall clock in the ICU room. This synchronization of watches between investigators helped to insure reliability of time notation.

Heart Rate and Rhythm Measurement

Heart rate and rhythm were measured continuously using a Hewlett Packard (HP M1175A) Component Monitoring System Model 54 with Electrocardiogram Module (HP M1001A)(Bellevue, Washington)(Figure 15). The module can record a heart rate range of 15-300 beats/min with accuracy of $\pm$ 1% of range, and the sensitivity is greater than 250 μV peak. Five electrodes were placed on the patient's chest. An adult Holter recorder (Model 90205 SpaceLabs, Redmond, WA) with a 24- or 48-hour cassette tape was inserted and used to record the channel 1 electrocardiogram from the Hewlett Packard monitor. A SpaceLabs FT

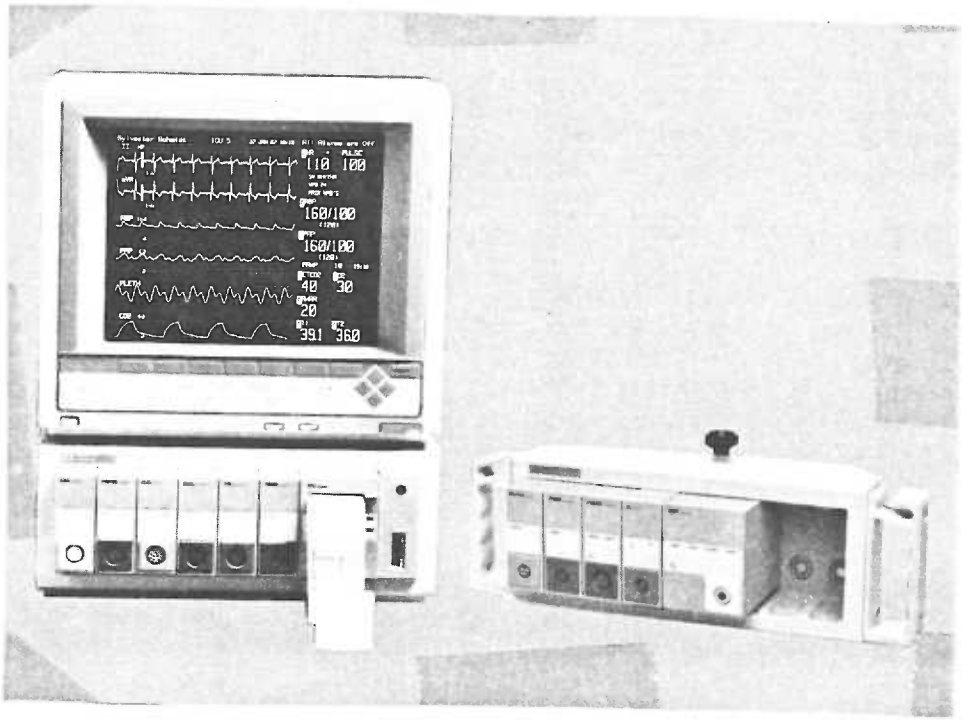


Figure 15. Hewlett Packard Component Monitoring System - Model 156. The Holter tape recorder cable was inserted into the synchronizer port of the cardiac monitor.

2000 Medical Analysis and Review Station (Model 90103) was used to scan the tapes. SpaceLabs' protocol for tape scanning was used and hard copies of tabular and histogram data, siginificant arrhythmias, and full disclosure (record of every beat) were obtained. Interrater reliability was established by comparing the reviews of one 48-hour tape by the investigator and a SpaceLabs' Senior Nurse Scanner. Interrater agreement was 96% for hourly heart rate calculations, the few differences found were small and were due to varying use of the "ignore" command. Agreement was 90% for arrhythmia diagnosis. Accuracy of tape recorder speed was checked by recording 48 hours of calibration pulses (1/sec) and scanning this tape with the FT 2000 and was found to be very accurate. Table 5 summarizes the validity and reliability of measurement of heart rate and rhythm, thermodilution cardiac output, and stroke volume.

Cardiac Output Measurement

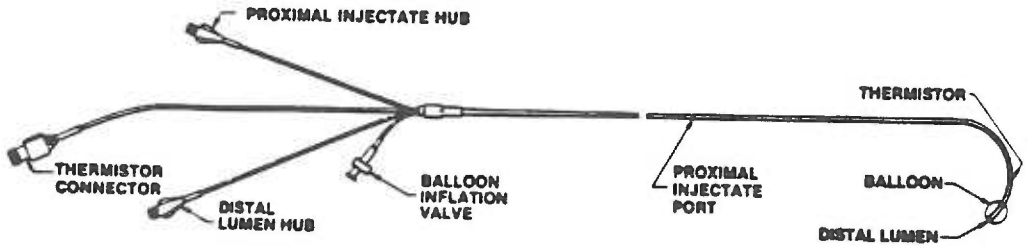
Cardiac output was measured using a Swan-Ganz^{R} Thermodilution Catheter (Model No. 93A-131-7F/131H)(Figure 16A), a VIP^{TM} catheter (Model No. 93A-831-7.5F/831H) (Baxter Healthcare Corporation, Edwards Critical Care Division, Santa Ana, CA), or an Opticath^{R} (Model No. P7110-7.5Fr)(Abbott Laboratories, Critical Care Systems) The "H" on the Swan-Ganz^{R} and VIP^{TM} catheters means that the catheters are heparin coated and the "F" number indicates the size of the catheter in French gauge units. A cardiac output computer (Model No. 9520A) (Figure 16B), CO-Set^{TM} II closed-injectate delivery system with iced injectate (Figure 17) (Model 93-500), and strip chart recorder (Model No. 9811) to analyze thermodilution curves were also used (Baxter Healthcare Corporation, Edwards Critical Care Division, Santa Ana,

Table 5

Validity and Reliability of Study Measurements

	Validity	Reliability
Heart rate and rhythm	-- Electrocardiogram (clinical gold standard) and tape recorded (criterion validity)	Interrater reliability of scanning technique
	-- Two-24 hr periods (internal validity)	
	-- Tape recorder speed checked using 48 hr of calibration pulses (1/sec) that were scanned by FT 2000	
Thermodilution cardiac output (CO)	-- Has compared well with clinical gold standard (Fick)(criterion validity)	Interrater reliability of CO measurement
	-- Accuracy checked by curve analysis (internal validity)	Interval consistency (same equipment)
	-- Two-24 hr periods (internal validity)	
Stroke volume (derived)	-- Two-24 hr periods (interval validity)	Intrarater reliability (deprivation repeated twice)
	-- Excluded subjects with atrial fibrillation (regular rhythm necessary to derive stroke volume)	

A.



B.

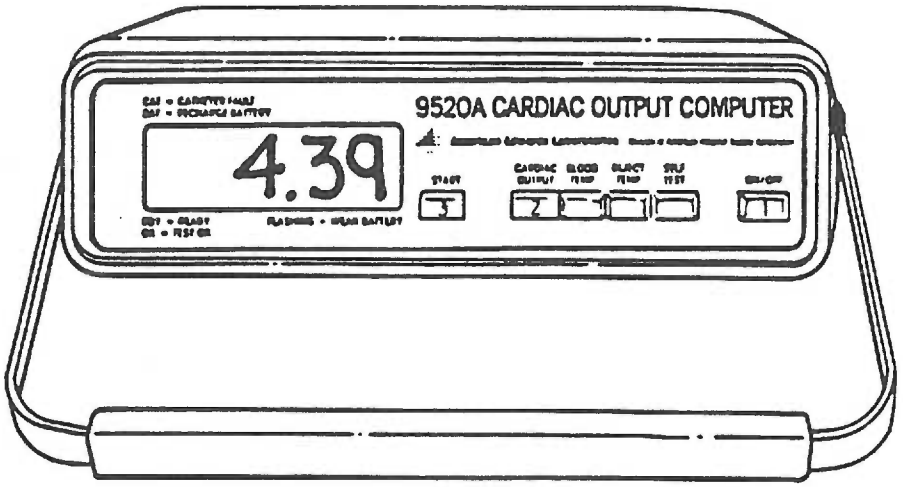


Figure 16. Cardiac output equipment: (A) Swan-Ganz® Thermodilution Pulmonary Artery Catheter. The proximal injectate lumen terminates 30 cm from the distal tip, opening into the right atrium. This lumen is used for injection of indicator solutions for cardiac output measurements. The thermistor lumen terminates in a thermistor sensor 4 cm from the distal tip. The electrical leads from this sensor terminate at the thermistor connector hub at the proximal end of the catheter. This hub is connected to a cardiac output computer when thermodilution cardiac output measurements are obtained. (B) Cardiac Output Computer. From Baxter Healthcare Corporation, Edwards Critical Care Division, Santa Ana, CA.

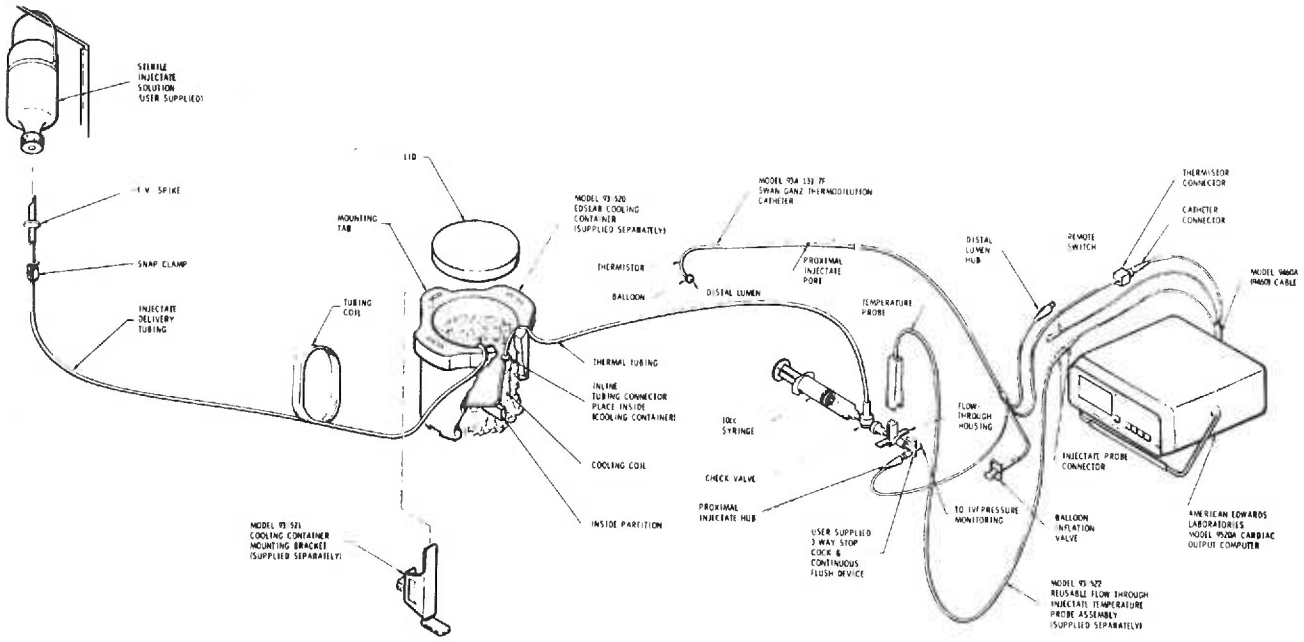


Figure 17. A schematic representation of a CO-Set^{R} (closed-injectate) delivery system for cardiac output measurement by thermodilution. From Baxter Healthcare Corporation, Edwards Critical Care Division, Santa Ana, CA.

CA). Digital cardiac output values were derived using a computer and the thermodilution curves were recorded on a strip chart recorder. The CO-Set^{TM} system used to deliver the bolus of cold solution used as a thermal indicator requires iced or room temperature injectate and has been shown to be a reliable method to obtain cardiac output measurements (Gardner, Monat, & Woods, 1987). The volume (5 or 10 ml) and the type of indicator solution (normal saline or 5% dextrose and water) were determined by the physician and were influenced by patients' fluid status. Use of saline instead of 5% dextrose and water has been shown to yield approximately 2% decrease in measured cardiac output. In the clinical setting, volumes of 5 ml and room temperature injectate may also be used (Merrick, Hessel, & Dillard, 1980; Swinney, Davenport, Wagers, Sebat, & Johnston, 1980; Kint, van Domburg, & Miy, 1981; Larson & Woods, 1982; Shellock, Riedinger, Bateman, & Gray, 1983; Shellock & Reidinger, 1983; Hruby & Woods, 1983; Vennix, Nelson, & Pierpont, 1984; Nelson & Anderson, 1985; Lyons & Dalbow, 1986; Davidson, Killpack, Woods, & McHugh, 1987; Gardner, Monat, & Woods, 1987). In this study 5 ml iced injectate was used, consistent with routine practice in this unit.

Prior to each cardiac output measurement, a computation constant was selected based on the type and size of pulmonary artery catheter and the temperature and volume of the injectate. For this study 0.259 was used for all catheters. The computation constant was then dialed into the computer. The thermistor connector cable from the computer was attached to the thermistor connector hub of the pulmonary catheter. Cardiac output was measured by first pressing the "start" button of the output computer, then injecting (beginning at the end of

inspiration) 5 ml iced injectate into the right atrium through the right atrial port of the pulmonary artery catheter (Armengol, Man, Balsys, & Wells, 1981; Jensen, Schreuder, Bogaard, van Rooyen, & Versprille, 1981; Snyder & Powner, 1982; Tajiri, Katsuya, Okamoto, Urata, & Sato, 1984; Lachenmyer & Stotts, 1985; Stevens, Raffin, Mihm, Rosenthal, & Stetz, 1985). If the patient was on a ventilator, the injection was made at the end of a ventilated breath. The syringe was handled minimally (to prevent thermal loss, i.e. warming of the solution) and the injection was given evenly and rapidly within 4 seconds. Pulmonary artery temperature was measured by the computer at baseline and frequently thereafter. The temperature change was then plotted over time by the computer, the area under the curve was calculated, and the cardiac output displayed digitally in l/min. A hard copy of the thermodilution curve was obtained using a strip chart recorder. Curves were examined visually to eliminate inaccurate measurements. A typical thermodilution time-temperature curve showed a smooth, rapid upslope to peak temperature and a gradual downslope to the point where computer data processing ended and extrapolation of the remainder of the curve occurred. (Figure 18A) Baseline respiratory oscillations may be evident on the curve recording. Figures 18B and C illustrate two distorted curves. Cardiac output was usually calculated as the average of three measurements that were within 10% of a median (middle) value (Weil, 1977) and was usually measured hourly in these critically ill adults. An injectate of 5 ml of 5% dextrose and water, or normal saline, if the patient had a low serum sodium, was used. Usually, three to five injections were delivered until three cardiac output values within 10% of a median

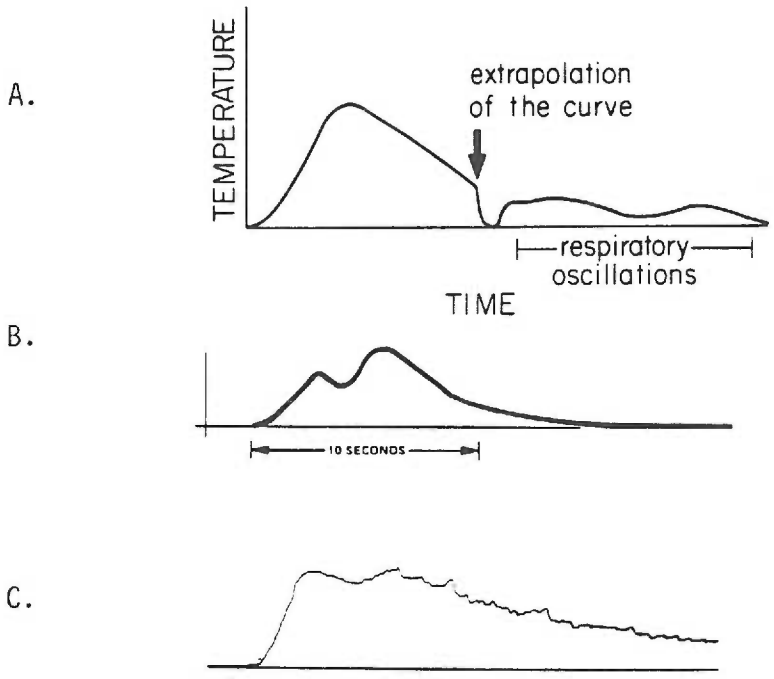


Figure 18. Thermodilution curves: (A) Normal and (B and C) Distorted. A typical thermodilution time-temperature curve (A) showing a smooth, rapid upslope to peak temperature and a gradual downslope to the point where computer data processing ends and extrapolation of the remainder of the curve occurs. Baseline respiratory oscillations are also evident on this curve recording. From "Current recommendations for thermodilution cardiac output measurement" by B. J. Loveys and S. L. Woods, 1986, Progress in Cardiovascular Nursing, 1, p. 25. Copyright 1986 by J. B. Lippincott Co. Reprinted by permission. (B) cardiac output time-temperature curve showing faulty injection technique. (Courtesy Hewlett-Packard, Inc.) (C) cardiac output time-temperature curve showing downslope distortion due to the thermistor being in contact with the pulmonary artery wall. From "Measurement of cardiac output by thermal dilution by M.E. Sanmarco, C.M. Philips, and L.A. Marquez et al., 1971, American Journal of Cardiology, 28, p. 57. Copyright 1971 by American Journal of Cardiology. Reprinted by permission.

value were averaged to obtain the cardiac output value (Weil, 1977). If after three to five injections, three values within 10% could not be obtained the three closest values were used. The same computer was used for the first five subjects; a second computer was used for the last subject. Thermodilution cardiac output measurements compared well with cardiac output measurements obtained with direct flow measurement, Fick method, and dye-dilution methods. Interrater agreement for cardiac output measurement was 90-100%. See Table 5 on page 67 for a summary of validity and reliability of the measurement of thermodilution cardiac output.

Stroke Volume Measurement

Stroke volume was derived from the cardiac output and heart rate values using the following formula:

$$\text{SV (ml/beat)} = \frac{\text{CO (ml/min)}}{\text{HR (beats/min)}}$$

Derivation was repeated twice to ensure accuracy.

See Table 5 on page 67 for summary of validity and reliability of derivation of stroke volume.

Data Collectors

The two investigators involved in data collection both had many years of ICU experience and experience obtaining cardiovascular measurements in both clinical and research settings. They served as non-participant observers recording environmental occurrences, as well as the physiological variables, over time. To verify reliability between these two nurses, a pilot study was conducted and percent agreement was calculated. Training continued until the following levels were reached: 100% agreement for heart rate and rhythm; 90-

100% agreement for cardiac output measurement; 80-100% for patient position and environmental events.

Light Intensity Measurement

A battery-powered light meter (Extech Digital) with a range of 0 to 50,000 LUX was used hourly and when lighting changed to measure light at the head of the patient's bed. The meter had a resolution of 0.1 foot-candle and accuracy of $\pm$ (5% + 2d). See Figure 19 for general specifications of this light meter.

Procedures

Prior to the study, classes regard the purpose and procedures of the study were presented to the nursing staff of the surgical ICU. The study was discussed with the physician in charge of this unit who requested that cardiac output measurement be made using an injectate of 5 ml of 5% dextrose and water and that measurements be obtained no more often than every 1-4 hours at the discretion of the patient's nurse. The physician gave permission to use three injections for each cardiac output measurement (two injections were standard in this unit).

Daily, one of the two investigators screened the patients on the preoperative cardiac unit and in the ICU for possible inclusion in the study. If a patient were eligible, the patient's nurse was asked to approach the patient to determine interest in discussing the study. If the patient was interested, the study was explained and written consent was obtained. Information about background variable was obtained from the patient's chart. The patient was not disturbed for data collection. Routine care was provided by the hospital staff and no attempt was made to control the environment. For each subject,

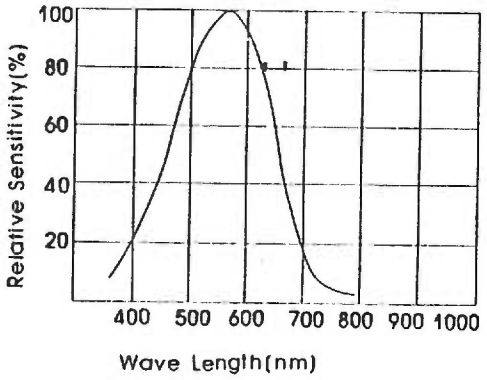
GENERAL SPECIFICATIONS

Display	13mm (0.5") LCD (Liquid Crystal Display).	Power Supply	006P DC 9V battery.
Measurement	Lux, Ft-candle.	Operating Temperature	0° to 50°C (32 to 122°F).
Ranges	Lux – 0 to 50,000 Lux, 3 ranges, Ft-candle – 0 to 5,000 Ft-candle, 3 ranges.	Operating Humidity	Less than 80% R.H.
Zero Adjustment	Automatic adjustment.	Dimension	163 x 70 x 30 mm (6.4 x 2.8 x 1.2 inch).
Over-input	Indication of "1".	Weight	220g (0.52 lb).
Sampling Time	Approx. 0.4 second.	Standard Accessories	Light sensor. . . . . 1 pc. Instruction Manual . . . . . 1 pc.
Sensor material	Selenium Photovoltaic Cells.		

ELECTRICAL SPECIFICATIONS

Range	Resolution	Accuracy (23 ± 5°C)	Range	Resolution	Accuracy (23 ± 5°C)
2,000 Lux	1 Lux	± (5% + 2d)	200 Ft-candle	0.1 Ft-candle	± (5% + 2d)
20,000 Lux	10 Lux	± (5% + 2d)	2,000 Ft-candle	1 Ft-candle	± (5% + 2d)
50,000 Lux	100 Lux	± (5% + 2d)	5,000 Ft-candle	10 Ft-candle	± (5% + 2d)

SPECTRUM FOR LIGHT SENSOR OF



CORRECTION FACTOR:

Mercury Lamp	x1.1
Fluorescent Lamp	x1.0
Incandesent Light	x1.0
Daylight	x1.0

Figure 19. Specifications for the Extech Digital Light Meter

two data collectors worked approximately 12-hour shifts (12 hours on, 12 hours off) for 24-48 hr. Each data collector collected data for both studies. Appendix H contains the detailed data collection protocol used for both this study and the concurrent study of body temperature.

Heart rate and rhythm were measured continuously using the Holter tape recorder. For the first three subjects, when 24-hour tapes were used, a 12-minute interruption occurred due to calibration between the two tapes. The last three subjects had 48-hour tapes, and no interruption was necessary. At a later time, the investigator analyzed the tapes using the SpaceLabs' FT 2000 (scanner) and protocol. Heart rate was calculated per minute and printed in histogram form and was averaged every 15 minutes by the scanner. Every 15 minutes, heart rate was recorded at the bedside from the digital display on the cardiac monitor and this heart rate value was used to derive stroke volume. Cardiac output was measured every 1-4 hours on the hour without altering the patient position (Prakash, Parmley, Dikshit, Forrester, & Swan 1973; Grose, Woods, & Laurent, 1981; Whitman, Howaniak, & Verga, 1982; and Kleven, 1984). If the patient could not have measurements taken on the hour, the measurements were obtained as soon as possible thereafter and the time noted. A minimum of 24 hours of data was collected on each subject.

To account for catheter dead space and the amount and temperature of the injectate, a computation constant was selected and dialed into the cardiac output computer (for 5 ml iced injectate - 0.259). Then the computer cable was attached to the pulmonary artery catheter thermistor lumen. Each 5 ml of iced injectate was injected within 4

seconds beginning at the end of inspiration to obtain three cardiac output values within 10% of a median value (Weil, 1977). A chart of 10% ranges of cardiac output was used to facilitate data collection (Appendix I). When "Ready" appeared on the computer, the next injection was made.

Internal and external patient environmental data thought to affect these physiological variables were noted on the data collection record. These data included illumination level, sounds, meals, medications, intravenous fluids, all treatments and procedures, baths, visitors, etc.

Light intensity was measured every hour on the hour and whenever lighting changed. The light meter sensor was placed parallel to the patient's face in the same direction as the patient's field of vision. After 5 seconds, the digital dial was read.

If the investigator left the patient's room, the time selected was between measurements of physiological variables when the activity in the room was quiet and the phrase "gap" and the exact time were written on the data collection form.

A pilot study was conducted to test the protocol for data collection and to calculate interrater reliability of measurements. Data were collected over a six-month period (1-19-90 through 6-27-90).

Protection of Human Subjects

Study procedures were approved by the Oregon Health Sciences University Committee on Human Research (Appendix J) and the institutional review board of the hospital. Approval was also obtained from the physician and the nurse in charge of the cardiac surgical intensive care unit. Written informed consent was obtained

preoperatively from the patient. The measurements of cardiac output, heart rate and rhythm, and temperature were routine in the care of critically ill adults. Thermodilution cardiac output measurements usually required 15-25 ml of intravenous fluid per measurement. Over a 24-hour period, if measurements were made hourly, this procedure could result in 360-600 ml of additional fluid. The patient's physician usually wrote an order for cardiac output measurement frequency, but the actual frequency was left up to the discretion of the patient's nurse. All data obtained was shared with nurses caring for the patient to eliminate duplication of measurements. There was no foreseen added risk to the patient for the study variables to be measured and recorded. If the physician decided that the patient could not tolerate the additional fluid associated with hourly cardiac output measurement, the frequency was reduced in accordance with the physician's orders. If the time interval between ordered measurements was greater than every four hours, however, the patient was not included in the sample.

The benefit of this research was a description of the temporal pattern of these variables. While the study did not benefit the patients directly, it provided information that may be of benefit to other patients in the future. Although the patient and family might have felt uncomfortable with the constant presence of the investigators, both in this study and in a recent similar study (L. Felver, personal communication, 1989), subjects were found to be appreciative of the investigator's presence. The patient's name did not appear on any of the data collection forms and all data were kept confidential by the investigators. The patient was free to withdraw

from the study at any time. Study data will be retained indefinitely and will be used in future related research.

Analysis of Data

Demographic data were analyzed using tables and descriptive statistics. Arrhythmias were analyzed by the investigator using the SpaceLabs' Medical Analysis and Review Stations Scanner and Protocol, and the electrocardiographic criteria listed in Appendix B. Study variables for each patient were described using graphs of the variables over time with treatment and environmental influences noted.

Cosinor analysis was used for each subject to determine if significant ($p<0.05$) ultradian and circadian rhythms existed in these cardiovascular variables. The regression equation is as follows:

$$Y_i = M + [A \cos (\theta + 2\pi t_i/\tau) + e_i]$$

where M = mesor, A = amplitude, cos = cosine, θ = computative acrophase, $2\pi/\tau$ = angular frequency, t = time, and e = error. From this analysis, the three parameters mesor, half-amplitude (mesor to acrophase), and acrophase were estimated by least squares fit of the cosine model with a fixed period as identified for the analysis.

$Y(t) = \beta_o + \beta_1 \text{ Cos } (2\pi) \text{ (t/period)} + \beta_2 \text{ Sin } (2\pi) \text{ (t/period)} + E$

t = time in decimal hours

Half-amplitude = $(\beta_1^2 + \beta_2^2)^{1/2}$

Acrophase = arctangent $(-\beta_2/\beta_1)$

Assumptions of cosinor analysis are that the period is known and that the data have a sinusoidal shape. Time periods used in the equation were determined after visualizing the graphic pattern of the variable concerned. Assumptions of regression analysis in general are that the residuals (errors) have the following characteristics: zero mean,

homogeneity of variance, independence, and normal distribution. (Bingham, Arbogast, Guillaume, Lee, & Halberg, 1982; DePrins, Cornelissen, & Malbecq, 1986)

F tests were used to test the hypothesis that the half-amplitude of the rhythm was equal to zero. A two-tailed probability level of 0.05 was used as the criterion for statistical significance. Levels greater than 0.05 but 0.10 or less were considered to indicate a trend toward significance. Significant single periods for each variable for each subject were groups and altogether placed in the regression equation and cosinor analysis repeated.

Acrophases for each variable were examined to determine overlap among subjects. Acrophases were referenced to subjects' customary midsleep time immediately prior to hospitalization. For one subject who had been in the hospital for two weeks, however, sleep time in the hospital prior to surgery was used. Heart rate and rhythm data for each subject were divided into two segments using criteria to be described in the results section and were analyzed by the cosinor procedures described above.

Cosinor analysis was completed on a Macintosh II computer (Apple Computer) using a Fortran (Language Systems Corporation) program written by Johannes (1984) and modified by Zucker, Reith, and Felver (L. Felver personal communication, 1990). To insure accuracy of calculations, cosinor analysis was repeated using Stat Works™ (Cricket Software) and an Excel (Microsoft Corporation) acrophase program written by Felver.

CHAPTER IV

RESULTS

To describe the temporal pattern in heart rate and rhythm, cardiac output, and stroke volume over 24 to 48 hours in critically ill adults in an intensive care unit (ICU), six patients were studied in the immediate postoperative period after cardiac surgery. A descriptive, time-series design was used. This chapter begins with a discussion of the characteristics of the sample followed by a description of the ICU routine the first 48 hours after cardiac surgery. Findings regarding the cardiovascular variables are then presented, with a concluding summary.

Sample Characteristics

Six adult patients in the cardiac ICU, one woman and five men were included in the study. Their ages ranged from 33-68 years, with a mean ($\pm$ 1 SD) of 48.3 $\pm$ 15.3 years. Table 6 summarizes each subject's surgical diagnosis, gender, and age. Height, weight, and calculated body surface area are listed in Table 7. Mean body surface area was 1.76 $\pm$ 0.15 m^2. Table 8 presents for all subjects, admission months and times, and time data collection began. Table 9 summarizes, for all subjects, time preference, customary time of sleep immediately prior to hospitalization, and an estimate of customary midsleep.

Subject 1 was a 33-year-old Caucasian man, who was admitted to the hospital in January 1990. He had mitral stenosis and insufficiency, mild aortic insufficiency, cardiomegaly, and pulmonary hypertension as well as a history of intravenous drug abuse, congestive heart failure, and a failed balloon-catheter mitral valvuloplasty. On the day after

Table 6

Diagnosis, Gender, and Age of Subjects

Subject	Cardiac Surgery	Gender	Age (yr)
1	Mitral valvuloplasty	male	33
2	CABG X 2 Aortic valve replacement	male	67
3	CABG X 4	female	37
4	CABG X 3	male	43
5	CABG X 1	male	42
6	CABG X 3	male	68

CABG, Coronary artery bypass graft

Table 7

Height, Weight, and Body Surface Area (Using Lean Body Weight) of Subjects

Subject	Weight (kg)	Height (in.)	%Fat=fat (kg)	Lean body weight (kg)	BSA(m^2)
1	79.0	72.0	11% = 8.69	70.3	1.92
2	79.8	68.0	17% = 13.57	66.2	1.80
3	69.5	64.0	18% = 12.51	57.0	1.61
4	89.1	69.5	22% = 19.60	69.5	1.87
5	65.4	63.0	18% = 11.77	53.6	1.55
6	75.0	69.0	14% = 10.50	64.5	1.80

BSA, body surface area.

Table 8

Days in Hospital Prior to Study and Time between ICU Admission and Start of Study

Subject	Month of hospital admission	Days in hospital prior to ICU admission	Time between ICU admission and study start
1	January	1	43 min
2	February	1	30 min
3	January	14	1 hr, 30 min
4	February	1	1 hr, 45 min
5	February	1	2 hr, 40 min
6	June	1	45 min

Table 9

Time Preference, Customary Sleep Time (Immediate Prehospital) and Customary Midsleep

Subject	Time preference	Customary bedtime	Normal awakening	Customary midsleep
1	Early morning	2200	0600	0200
2	Late morning	2200	0800	0300
3	Late morning to early afternoon	2300	0800	0330
4	Late morning to early afternoon	2400	0800	0400
5	Early morning	2200	0600	0200
6	Late afternoon to evening	0400	1000	0700

hospital admission he had a mitral valvuloplasty and commissurotomy that began at 1545. He was admitted to the ICU at 2115 and data collection began at 2200. He was a fisherman who worked 16-hour shifts. His sleep schedule varied when he was at work; his last work was in December, 1989. Prior to hospitalization, he was usually an early morning riser (0600) and went to bed around 2200. Digoxin was the only medication he took prior to hospitalization, and this medication was continued during hospitalization. He had difficulty hearing from his right ear, but had no other sensory deficits.

Subject 2 was a 67-year-old Caucasian male who was admitted to the hospital in February 1990. He had coronary heart disease (CHD) and rest angina. He had had an aortic valve replacement 7 years ago and the valve was in need of replacement. He had a history of a hiatal hernia and right inguinal hernia. Two weeks prior to this admission he was in the hospital for an unknown length of time for a ruled out myocardial infarction (MI). On the day after the present hospital admission he had an aortic valve replacement and coronary artery bypass graft (CABG) surgery that began at 0835. He was admitted to the ICU at 1600 and data collection began at 1630. He was a retired engineer. After retirement, he continued to be up early (0800) and to retire early (2200). Verapamil was the only medication he was taking prior to hospital admission and this medication was not given during the time of the study. He was started on digoxin after hospitalization. He wore glasses, but had no other sensory deficits.

Subject 3 was a 37-year-old Caucasian woman who was admitted to the hospital in January 1990. She had CHD and unstable angina, and a

history of insulin-dependent diabetes mellitus for 24 years, hypertension, renal failure, and an MI in February 1989. Fourteen days after hospitalization she had CABG surgery that started at 1000. She was admitted to the ICU at 1630 and data collection began at 1800. She was a married housewife with no children. She was usually up by 0800 and was in bed by 2300. Prior to hospitalization, she was taking the following medications: furosemide, acetylsalicylic acid, cholestyramine resin, metalozone, isosorbide dinitrate, diltiazem, metoprolol, estrogen, and insulin. Once admitted, she was started on nifedipine, clonidine, insulin, and Ecotrin^{R}; all other medications were discontinued. She wore glasses but had no other sensory deficits.

Subject 4 was a 43-year-old Hispanic man who was admitted in February 1990. He had CHD and probable peptic ulcer disease. The day after hospitalization, he had CABG surgery that began at 0800. He was admitted to the ICU at 1200 and data collection began at 1345. He was a disabled farm worker who had not worked since he had a work-related injury. He went to bed about 2400 and awoke at 0800. Prior to hospitalization he was taking atenolol and diltiazem, and these medications were discontinued during hospitalization. After hospitalization, he was started on: digoxin, ranitidine hydrochloride, metoclopramine, nitroglycerin, and diazepam. He had no known sensory deficits.

Subject 5 was a 42-year-old Hispanic man who was admitted in February. He had CHD and a history of previous CABG surgery, MI, and diabetes mellitus. He had CABG surgery on the day after admission

(0830-1115). He was admitted to the ICU at 1120 and data collection began at 1400. He did not work. He went to bed by 2200 and awoke at 0600. Prior to hospitalization he was taking the following medications: nitroglycerin, acetylsalicylic acid, isosorbide dinitrate, metoprolol, diltiazem, and glydiazenamide. During hospitalization he was started on digoxin and ranitidine, and other medications were discontinued. He had no known sensory deficits.

Subject 6 was a 68-year-old Caucasian man who was admitted in June 1990. He had CHD, an MI 6 weeks previously, and a cerebral vascular accident 2 weeks previously. He had a history of adult-onset diabetes mellitus and hypertension. On the day after admission, he had CABG surgery that began at 0830. He was admitted to ICU at 1414 and data collection began at 1500. He was retired, but had been an evening and night worker. After retirement, he maintained a sleep schedule of 0400 to 1000 and always kept a light on during sleep. Prior to hospitalization, he was taking nifedipine, zestril, nitroglycerin, and an oral hypoglycemic. During hospitalization he was started on digoxin and other medications were discontinued. He wore glasses and had moderate difficulty hearing.

Cardiac Surgical Intensive Care Unit Routine

After cardiac surgery, patients were admitted directly to the cardiac ICU for anesthesia recovery and for intensive care for three to five days. Patients were admitted to the ICU with an endotracheal tube in place and manual artificial breathing using an anesthesia bag. Patients were unconscious and apneic and were immediately attached to a ventilator for respirations. Initially, the oxygen concentration was

usually 100% and positive end-expiratory pressure (PEEP) of 5-10 cm of water pressure was applied. Electrocardiographic chest electrodes were applied on the chest. Leads used for monitoring varied due to chest dressing placement. Patients were then attached to pressure monitoring devices (pulmonary artery pressure, arterial blood pressure, and central venous pressure), and to cardiac output equipment. Vasoactive intravenous drips (nitroglycerin, nitroprusside, isoproterenol, dopamine) were continued at rates ordered by the physician. Chest tubes (pleural and mediastinal) and drainage system, and urinary catheter and drainage system were attached to the patient and bed. Transthoracic pacer electrode wires were attached to a pulse generator set to the demand mode.

Vital signs were then obtained and a complete nursing assessment begun. Data collection for the study began during this phase of ICU admission, starting 43 minutes to 2 hours, 40 minutes after ICU admission. Table 10 summarizes each patient's initial treatment. The first five subjects were studied in the winter; Subject 6 was studied in the summer.

Temporal Pattern in Heart Rate and Rhythm

Holter tape recordings of heart rate and rhythm were obtained on each subject for 48 hours. Not all data were included in analysis and the criteria used to exclude data from the analysis are summarized in Table 11. Since changes in heart rate and body temperature follow each other closely, heart rate data were excluded until pulmonary artery temperature reached 37°C. One subject had bradycardia on admission to ICU and needed pacing. Pacing data were excluded from analysis.

Table 10

Level of Consciousness and Therapy At Start of Data Collection

Subject	Glasgow coma scale (0-15)	Intubated	Oxygen (%)	PEEP (cm H_2O)	Vasoactive IV medication	IV fluid
1	3	yes	100	5	nitroprusside 200 mg/250 ml D_5W - 9ml/hr	plasma protein fraction - 150 ml/hr
					dopamine 400 mg/250 ml D_5W - 15 ml/hr	D_5W - 17 ml/hr
2	3	yes	100	5	nitroprusside 400 mg/250ml D_5W - 1.2 ml/hr	plasma protein fraction - wide open
					dopamine 900 mg/250ml D_5W - 4 ml/hr	D_5W - 20 ml/hr
3	3	yes	100	5	nitroglycerin 100 mg/250 ml D_5W - 2 ml/hr	plasma protein fraction - fast
					nitroprusside 250 mg/250 ml D_5W - 8 ml/hr	D_5W - 30 ml/hr
					isoproterenol 5 mg/250 ml D_5W - 1 ml/hr	
4	3	yes	70	5	none	D_5W - 41 ml/hr
5	3	yes	100	5	nitroprusside 250 mg/250 ml D_5W - 2 ml/hr	plasma protein fraction - wide open
						D_5W - 21 ml/hr
6	3	yes	100	5	isoproterenol 5 mg/250 ml D_5W - 2 ml/hr	plasma protein fraction - wide open saline 41 ml/hr

Table 11

Criteria Used to Delete Initial Data from Analysis

Subject	Criteria
1	Data deleted until PA temperature was 37°C
2	Data deleted until PA temperature was 37°C
3	Data deleted until PA temperature was 37°C
4	Data deleted until PA temperature was 37°C
5	Data deleted until PA temperature was 37°C and fluid resuscitation was completed
6	Data deleted until pacemaker turned off and PA temperature was 37°C

PA = pulmonary artery

Table 12 lists for each subject the total number of hours used for data analysis.

Graphical Analysis of Heart Rate and Rhythm

Continuous heart rate was averaged every 15 minutes using the electroradiographic scanner (FT2000) and graphed over time (Figures 20). Episodes of arrhythmias in a 15-minute period were also graphed over time for the four subjects that had enough arrhythmias for meaningful analysis (Figure 21). Treatment and environment variables were also noted on the graphs. Variables thought to affect heart rate and rhythm greatly were examined to determine effect. Next, increases and decreases in heart rate and arrhythmia occurrences were examined to see if a relationship between environmental or treatment variables was apparent. See Appendix J for an example of this analysis. On two occasions heart data were excluded due to known effect of a bolus of intravenous (IV) nitroprusside (Subject 3) and a bolus of IV isoproterenol (Subject 6) on heart rate. Both drugs act immediately and the effects of isoproterenol can last 1-2 hours, effectiveness of IV nitroprusside ends when the drug is stopped.

Arrhythmias graphed for the four subjects included: Subject 1, premature atrial contractions (PACs), atrial tachycardia, premature ventricular contractions (PVCs), ventricular couplets, and ventricular tachycardia (VT); for Subjects 2 and 3 PACs and PVCs; and for Subject 6 PVCs, ventricular couplets, and VT. Subject 4 had a total of 11 PACs and 10 PVCs in 48 hours; and Subject 5 had a total of 3 PACs and 8 PVCs in 48 hours, therefore these data were not analyzed further.

Graphed data show showed much fluctuation over time in heart rate

Table 12

Total Number of Hours of Heart Rate and Rhythm Data Used for Analysis

Subject	Data collection time	Total
1	Day 1 23.50 through Day 3 22.00	46.50 hr
2	Day 1 18.25 through Day 3 16.50	46.25 hr
3	Day 1 22.75 through Day 3 18.75	44.00 hr
4	Day 1 15.75 through Day 3 13.75	46.00 hr
5	Day 1 18.00 through Day 3 13.50	43.50 hr
6	Day 1 18.25 through Day 3 14.50	44.25 hr

Note. Time is given in decimal hours.

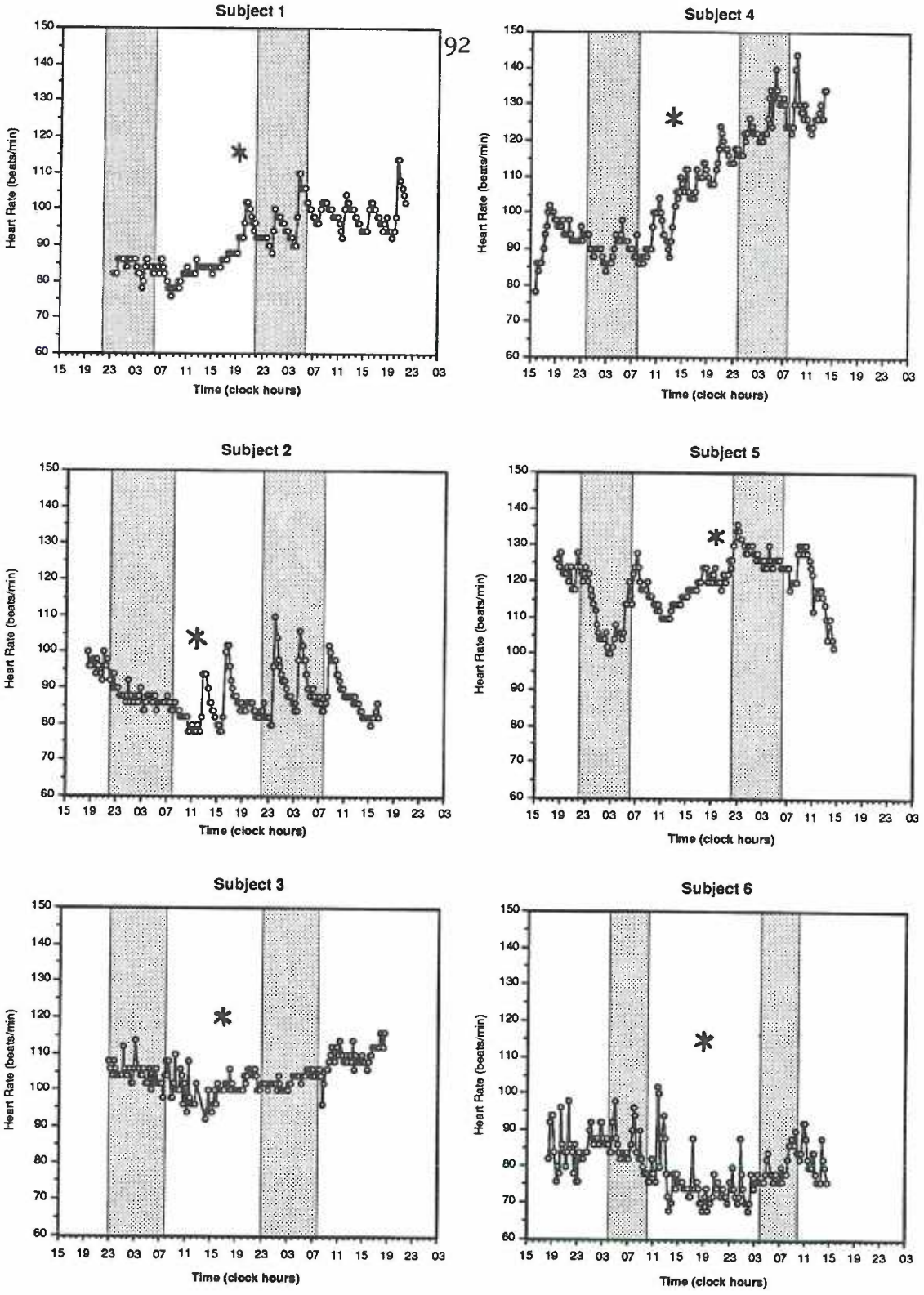


Figure 20. Graphs of 15-minute averaged heart rate data over time (N=6). Customary sleep time is shaded; this was not the sleep time during the study. Star indicates where data were divided.

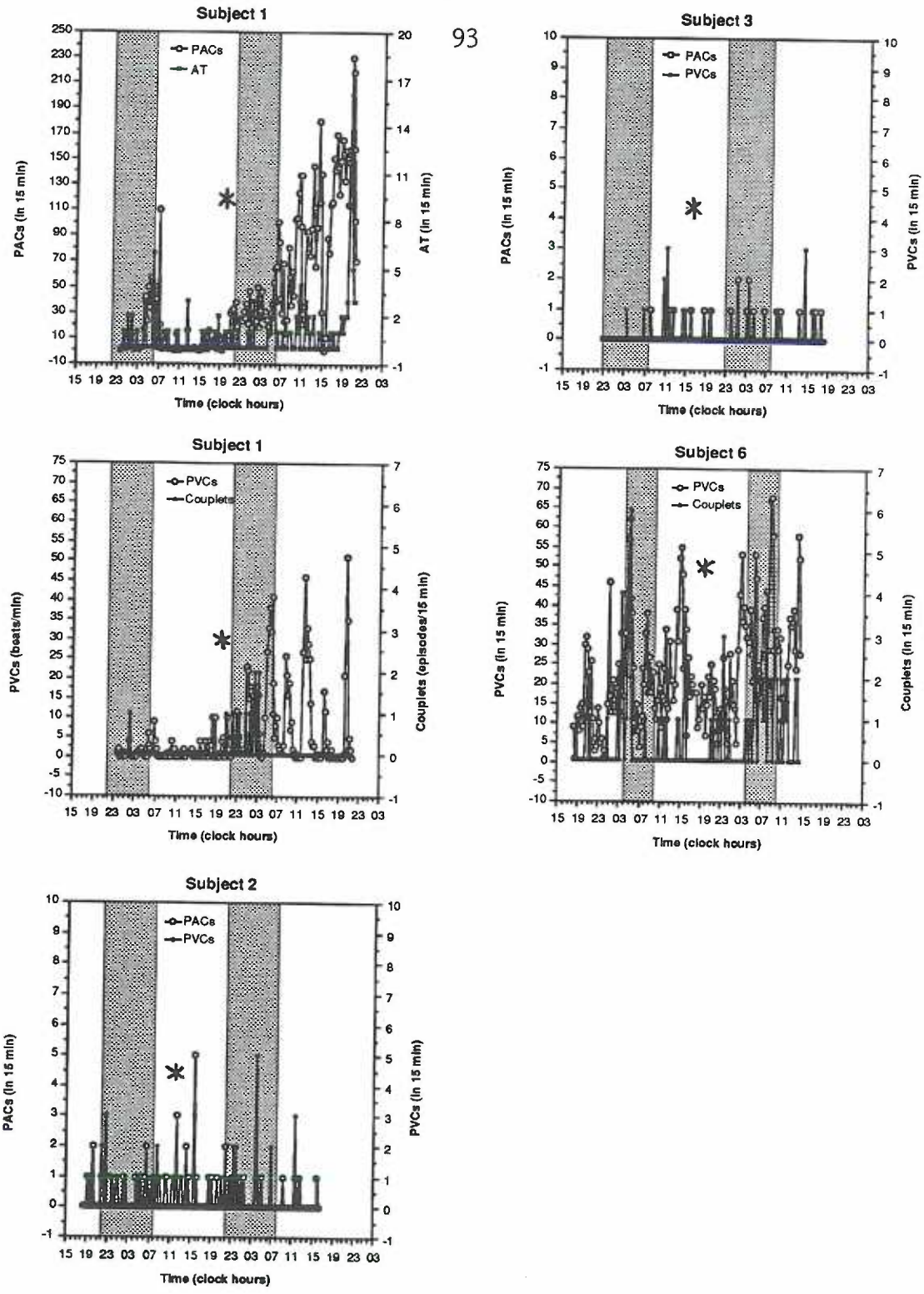


Figure 21. Graphs of arrhythmias over time (n=4). Customary sleep time is shaded; this was not the sleep time during the study. Star indicates where data were divided.

and occurrence of arrhythmias. Single environmental effects on heart rate and rhythm were difficult to isolate. Many factors together appeared to influence the observed heart rate and rhythm. However, an increase in heart rate was consistently seen on the graphs in all individuals (n=5) who received chest physiotherapy, inhalations of a bronchodilator, or both. Usually, the respiratory therapy treatment began after extubation and was repeated approximately every 4 hours. First, the lungs were auscultated and a bronchodilator was administered over 10 minutes by inhalation. Usually metaproterenol, or occasionally albuterol was used, both of which are beta-2 adrenergic receptor agonists that act in about 30-40 minutes and last 1-5 hours (metaproterenol) or 3-6 hours (albuterol). After inhalation, the patient was encouraged to cough and deep breathe. Chest physiotherapy followed, which usually involved positioning the patient flat, or with head down, and turning the patient to each side, while the chest was vibrated for about five minutes. The patient was then repositioned for comfort and was asked to use the incentive spirometer.

Patients were usually very tired after the therapy. The total number of treatments for the five subjects was 23. All five experienced an increase in heart rate of 1-29 beats per minutes (Table 13). Most increases were clinically significant (increase of 10 beats or more per minute). In those whose heart rate returned to pretherapy levels before the next treatment, 15 minutes to 2 hours, and 45 minutes (mean time was 1 hr 45 min $\pm$ 52 min) was required for the heart rate to return to pretherapy levels. Over the period of observation, there were instances when heart rate never returned to the pretherapy level. Three subjects

Table 13

Effects of Respiratory Therapy on Heart Rate and Rhythm

Patient number	Treatment	Study day	Time of metaproterenol administration	Predose HR in beats per min (time)	HR 5-15 minutes after beginning of dose (time)	Peak HR (time)	Minutes to peak HR	Change in HR (beats/min)	Time of return to predose HR prior to next treatment (HR)	Minutes to reach predose HR from peak HR	Arrhythmia
1	B	1	2005-2016	95(2000)	97(2015)	109(2030)	25	14	2200(96)	1 hr 45 min	PACs and PVCs
	B	2	0045-0055	91(0045)	98(0100)	101(0130)	45	10	0330(91)	2 hr	PACs and PVCs
	B	2	0430-0440	93(0430)	105(0445)	112(0500)	30	19	never	---	PACs and PVCs
	B	2	0815-0825	97(0745)	102(0830)	102(0830)	15	4	1045(98)	2 hr 15 min	PACs and PVCs
	B	2	1200-1210	94(1200)	105(1215)	106(1230)	30	12	1445(96)	2 hr 15 min	PACs and PVCs
	B	2	1554-1604	94(1545)	102(1615)	104(1630)	36	10	1915(95)	2 hr 45 min	PACs and PVCs
	B	2	2020-2028	96(2015)	108(2030)	120(2100)	50	24	never	---	PACs and PVCs
2	B	1	1226-1236	82(1215)	95(1245)	96(1315)	49	14	1500(82)	1 hr 45 min	PVCs
	B	1	1600-1610	80(1600)	104(1615)	105(1630)	33	24	never	---	PVCs
	CP	1	CP-1927	PreCP-86(1915)	PreCP-85(1930)	87(2000)	45	1	2030(86)	30 min	PVCs
	B	1	2345-2355	82(2345)	106(2400)	111(0015)	30	29	never	---	PVCs
	B	2	0342-0351	86(0330)	87(0345)	108(0415)	33	22	0645(87)	2 hr 30 min	PVCs
	B(Albuterol)	2	0823-0833	88(0815)	89(0830)	103(0845)	22	15	1115(87)	2 hr 30 min	
	CP	2	CP-1600	PreCP-83(1600)	PreCP-86(1615)	87(1630)	30	4	data collection ended		PVCs
4	B	1	1325-1336	91(1315)	96(1330)	109(1415)	50	18	never	---	
	M	1	1655-1706	101(1645)	106(1700)	115(1715)	20	14	never	---	
	M	1	2034-2046	107(2030)	120(2045)	125(2100)	26	18	never	---	
	B	2	0027-0039	115(0015)	118(0030)	128(0100)	33	13	never	---	
	B	2	0519-0539	125(0515)	133(0530)	150(0545)	25	25	0730(126)	1 hr 45 min	
	B(Albuterol)	2	0848-0901	127(0845)	133(0900)	149(0915)	27	22	1000(128)	45 min	
	B(Albuterol)	2	1311-1324	132(1300)	128(1315)	136(1345)	34	4	data collection ended		
5	CP	2	CP-2213	PreCP-127(2200)	PreCP-130(2215)	137(2245)	32	10	data collection ended		
6	CP	2	CP-1340	PreCP- 79(1330)	PreCP-74(1345)	94(1400)	20	15	1415(79)	15 min	PVCs and VT

HR, heart rate; PACs, premature atrial contractions; PVCs, premature ventricular contractions; VT, ventricular tachycardia.

Note. Treatments are coded as follows: B, Metaproterenol and chest physiotherapy; M, Metaproterenol only; CP, Chest physiotherapy only

that had one treatment of chest physiotherapy without the administration of a bronchodilator had smaller increases in heart rate (1-15 beats per minute) and a more rapid return to pretreatment levels (15-30 minutes). For Subject 4 who received two treatments with metaproterenol only, heart rates increased 14-18 beats per minute and did not return to pretherapy levels during the period of observation. While with albuterol only, heart rates increased 4-22 beats per minute and returned to pretherapy levels in 1 hour to 2 hours, 45 minutes. Subjects who had arrhythmias (PACs, PVCs, and VT), experienced an increased occurrence of these events with respiratory therapy, with the exception of one occasion in which the bronchodilator used was albuterol instead of the usual metaproterenol.

Increases in heart rate and occurrence of arrhythmias were also seen with endotracheal suctioning, extubation, position change (repositioning in bed, dangling, up in chair), shivering, bed bath, vomiting, and discontinuation of tubes and catheters (chest tubes, urinary catheter, pulmonary artery and arterial catheters, nasogastric tube). Subjects were also awakened frequently during these first two postoperative days. A relationship between awakenings and changes in these cardiovascular variables was difficult to isolate.

The heart rate generally changed over the data collection period. All subjects, except Subject 6, had a higher heart rate during the second segment of data collection (postextubation) compared to first segment (preextubation). (Subject 6 was not extubated until late in the data collection period so a midpoint was selected.) After endotracheal extubation, heart rate changed. Subject 6 was receiving intravenous

isoproterenol during the first part of data collection. Isoproterenol is a cardiac beta receptor agonist and has positive chronotrophic effects (increases heart rate). Fifteen-minute averaged heart rates for the first and second segments of the data are summarized below.

Subject	HR-first segment (beats/min)	HR-second segment (beats/min)
1	76-88	88-114
2	78-100	78-110
3	92-114	96-116
4	78-104	96-144
5	102-126	102-136
6	72-102	68-92

Subject 1 had more arrhythmias during the second segment of data collection while Subject 3 had less. Subject 2 and 6 had arrhythmias throughout the data collection period.

When the graphs were inspected for rhythmic fluctuations large peaks in heart rate were seen in Subjects 1, 2, and 4 that corresponded with the time of respiratory therapy. Also, heart rate was expected to decrease during an individual's prehospital, customary sleep time. This expected decrease did not occur for Subjects 1 and 6. For Subjects 2, 4, and 5, heart rate decreased when expected during the first segment of data collection but not during the second segment. For Subject 3, heart rate decreased during customary sleep time only during the second segment of data collection. In normal subjects, heart rate was expected to peak 9.75-18.75 hours after midsleep. This peaking was not always visible on the graphs. Subject 4 seemed to have peaks when expected (Figure 20). Arrhythmias were expected to increase during the activity period and decrease during customary sleep time, but no such pattern

could be identified from the graphs (Figure 21).

Cosinor Analysis of Heart Rate Data

Whole Data Set Analysis

Cosinor analysis of heart rate data revealed significant 24-hour rhythms ($p<0.056$; R^2=3.1%-8.8%) in all but Subject 3. Subjects 1 and 5 had significant 12-hour rhythms as well ($p<0.058$; R^2=3.1%-15.1%). Subjects 1 and 2 had significant 4-hour rhythms ($p<0.014$; R^2=4.5%-11.8%). No 1.5-hour or 6-hour rhythms were found. Table 14 summarizes the cosinor analysis of heart rate data for each subject. When multiple periods were analyzed together for a variable for a subject, the explained variance increased (R^2 ranged from 11.0%-21.9%).

For 24-hour rhythms, mesors ($\pm$ SE) ranged from 80 $\pm$ 0.5 to 119 $\pm$ 0.6 beats/min and half-amplitudes ($\pm$ SE) (mesor to peak of cosine curve) varied from 2 $\pm$ 0.8 to 4 $\pm$ 1.7 beats/min. Acrophases for the 24-hour rhythms, calculated as hours after customary midsleep, were somewhat variable (Table 15). Only one acrophase occurred when expected (9.75-18.75 hours after customary midsleep), Subject 1. Subjects 2 and 5 had overlapping acrophases.

For 12-hour periods, mesors and half-amplitudes were similar to those with 24-hour rhythms, mesors ranged from 92 $\pm$ 0.6 to 119 $\pm$ 0.5 beats/min and half-amplitudes ranged from 2 $\pm$ 0.9 to 4 $\pm$ 0.8 beats/min. Subjects 1 and 5 had overlapping acrophases. One of Subject 1's 12-hour-rhythm acrophases overlapped with his 24-hour-rhythm-acrophase.

For 4-hour rhythms (n=2), mesors ranged from 88 $\pm$ 0.4 to 92 $\pm$ 0.6 beats/min. Amplitudes ranged from 2 $\pm$ 1 to 3 $\pm$ 1 beats/min.

Table 14

Cosinor Analysis of Continuous Heart Rate Data (15 Minute Averages)

Subject	Period (hr)	Probability	R^2	Mesor ± SE rounded to nearest beat (beats/min)	Half-amplitude (mesor to peak) ± SE rounded to nearest beat (beats/min)	Acrophase ± SE (clock hr)	Acrophase (hr after customary midsleep)
1	24	0.034*	3.6%	92 ± 0.6	2 ± 0.8	2033 ± 1 hr, 26 min	18 hr, 33 min ± 1 hr, 26 min
	12	0.058+	3.1%	92 ± 0.6	2 ± 0.9	0802 ± 49 min	6 hr, 2 min ± 49 min
						2002 ± 49 min	18 hr, 2 min ± 49 min
	4	0.014*	4.5%	92 ± 0.6	2 ± 0.8	0113 ± 13 min	23 hr, 13 min ± 13 min
						0513 ± 13 min	3 hr, 13 min ± 13 min
						0913 ± 13 min	7 hr, 13 min ± 13 min
						1313 ± 13 min	11 hr, 13 min ± 13 min
						1713 ± 13 min	15 hr, 13 min ± 13 min
						2113 ± 13 min	19 hr, 13 min ± 13 min
	24,12,4	0.002**	11%	92 ± 0.6	2 (24 hr)	2027	18 hr, 27 min
					2 (12 hr)	0803	6 hr, 3 min
						2003	18 hr, 3 min
					2 (4 hr)	0046	22 hr, 46 min
						0446	2 hr, 46 min
						0846	6 hr, 46 min
						1246	10 hr, 46 min
						1646	14 hr, 46 min
						2046	18 hr, 46 min

table continues

Table 14 (continued)

Subject	Period (hr)	Probability	R^2	Mesor ± SE rounded to nearest beat (beats/min)	Half-amplitude (mesor to peak) ± SE rounded to nearest beat beats/min)	Acrophase ± SE (clock hr)	Acrophase (hr after customary midsleep)
2	24	0.001***	7.1%	88 ± 0.4	2 ± 0.6	0008 ± 1 hr, 3 min	21 hr, 8 min ± 1 hr, 3 min
	12	NS					
	4	0.000***	11.8%	88 ± 0.4	3 ± 0.6	0048 ± 8 min	21 hr, 48 min ± 8 min
						0448 ± 8 min	1 hr, 48 min ± 8 min
						0848 ± 8 min	5 hr, 48 min ± 8 min
						1248 ± 8 min	9 hr, 48 min ± 8 min
						1648 ± 8 min	13 hr, 48 min ± 8 min
						2048 ± 8 min	17 hr, 48 min ± 8 min
	24,4	0.000***	18.8%	88 ± 0.4	2 (24 hr)	0001	21 hr, 1 min
					3 (4 hr)	0047	21 hr, 47 min
						0447	1 hr, 47 min
						0847	5 hr, 47 min
						1247	9 hr, 47 min
						1647	13 hr, 47 min
						2047	17 hr, 47 min
3	24	NS					
	12	NS					
	4	NS					
4	24	0.056+	3.1%	107 ± 1.2	4 ± 1.7	0825 ± 1 hr 38 min	4 hr, 25 min ± 1 hr, 38 min
	12	NS					
	4	NS					

table continues

Table 14 (continued)

Subject	Period (hr)	Probability	R^2	Mesor ± SE rounded to nearest beat (beats/min)	Half-amplitude (mesor to peak) ± SE rounded to nearest beat (beats/min)	Acrophase ± SE (clock hr)	Acrophase (hr after customary midsleep)
5	24	0.007**	5.5%	119 ± 0.6	2 ± 0.8	2243 ± 1 hr, 18 min	20 hr, 43 min ± 1 hr, 18 min
	12	0.000***	15.9%	119 ± 0.5	4 ± 0.8	0812 ± 20 min 2012 ± 20 min	6 hr, 12 min ± 20 min 18 hr, 12 min ± 20 min
	4	NS					
	24,12	0.000***	21.9%	119 ± 0.5	3 (24 hr)	2315	21 hr, 15 min
					4 (4 hr)	0821 2021	6 hr, 21 min 18 hr, 21 min
6	24	0.000***	8.8%	80 ± 0.5	3 ± 0.8	0716 ± 56 min	16 min ± 56 min
	12	NS					
	4	NS					

NS = nonsignificant + = p< 0.10 (trend) * = p< 0.05 ** = p< 0.01 *** = p< .001

Table 15

Acrophase and Standard Error for Significant Periods in Heart Rate Data

Subject	Period	Acrophase ± SE (hr after customary midsleep)	Acrophase ± SE (decimal hr after customary midsleep)
1	24	18 hr, 33 min ± 1 hr, 26 min	18.55 ± 1.43(17.12-19.98)
	12	6 hr, 2 min ± 49 min	6.03 ± 0.82(5.21-6.85)
		18 hr, 2 min ± 49 min	18.03 ± 0.82(17.21-18.85)
	4	23 hr, 13 min ± 13 min	23.22 ± 0.22(23.00-23.44)
		3 hr, 13 min ± 13 min	3.22 ± 0.22(3.00-03.44)
		7 hr, 13 min ± 13 min	7.22 ± 0.22(7.00-07.44)
		11 hr, 13 min ± 13 min	11.22 ± 0.22(11.00-11.44)
		15 hr, 13 min ± 13 min	15.22 ± 0.22(15.00-15.44)
		19 hr, 13 min ± 13 min	19.22 ± 0.22(19.00-19.44)
2	24	21 hr, 8 min ± 1 hr, 3 min	21.13 ± 1.05(20.08-22.18)
	4	21 hr, 48 min ± 8 min	21.80 ± 0.13(21.67-21.93)
		1 hr, 48 min ± 8 min	1.80 ± 0.13(1.67-01.93)
		5 hr, 48 min ± 8 min	5.80 ± 0.13(5.67-05.93)
		9 hr, 48 min ± 8 min	9.80 ± 0.13(9.67-09.93)
		13 hr, 48 min ± 8 min	13.80 ± 0.13(13.67-13.93)
		17 hr, 48 min ± 8 min	17.80 ± 0.13(17.67-17.93)
4	24	4 hr, 25 min ± 1 hr, 38 min	4.42 ± 1.63(2.79-06.05)
5	24	20 hr, 43 min ± 1 hr, 18 min	20.72 ± 1.30(19.42-22.02)
	12	6 hr, 12 min ± 20 min	6.20 ± 0.33(5.87-06.53)
		18 hr, 12 min ± 20 min	18.20 ± 0.33(17.87-18.53)
6	24	16 min ± 56 min	0.27 ± 0.93(23.34-25.20)

SE, Standard error

Acrophases were nonoverlapping.

Mesors, amplitudes, and acrophases for the significant periods (n=3) added together in one multiple-period cosinor analysis were similar to those obtained from the single-period cosinor analysis. For Subject 1, 24-hour, 12-hour, and 4-hour periods were used together; for Subject 2, 24-hour, and 4-hour periods were used; and for Subject 5, 24-hour and 12-hour periods were used. Figures 22-24 illustrate the fitted cosine curves on the heart rate graph of each subject for all significant periods.

Divided Data Set Analysis

Because overall heart rate was different in the first segment of the data compared to the second segment of data, cosinor analysis was repeated on each segment. Since 48 hours of data were not available for each subject, data could not be divided into two 24-hour segments. Instead, clinical criteria were used to divide data into two segments. Extubation and the initiation of respiratory therapy seemed to be an appropriate time to split data since mean heart rate changed at that point. Table 16 summarizes the criteria used for each subject and the duration of each segment.

Cosinor analysis of divided heart rate data revealed significant 24-hour rhythms (or a trend toward significance $p \leq 0.10$) in Segments A and B for all subjects (Table 17). Subject 3 did not have a significant 24-hour rhythm when the data were analyzed as a whole, but did in both segments when data were divided into two segments.

Twelve-hour rhythms were found in both Segments A and B, and in the whole data analysis in Subject 1. In Subject 2, a 12-hour rhythm was

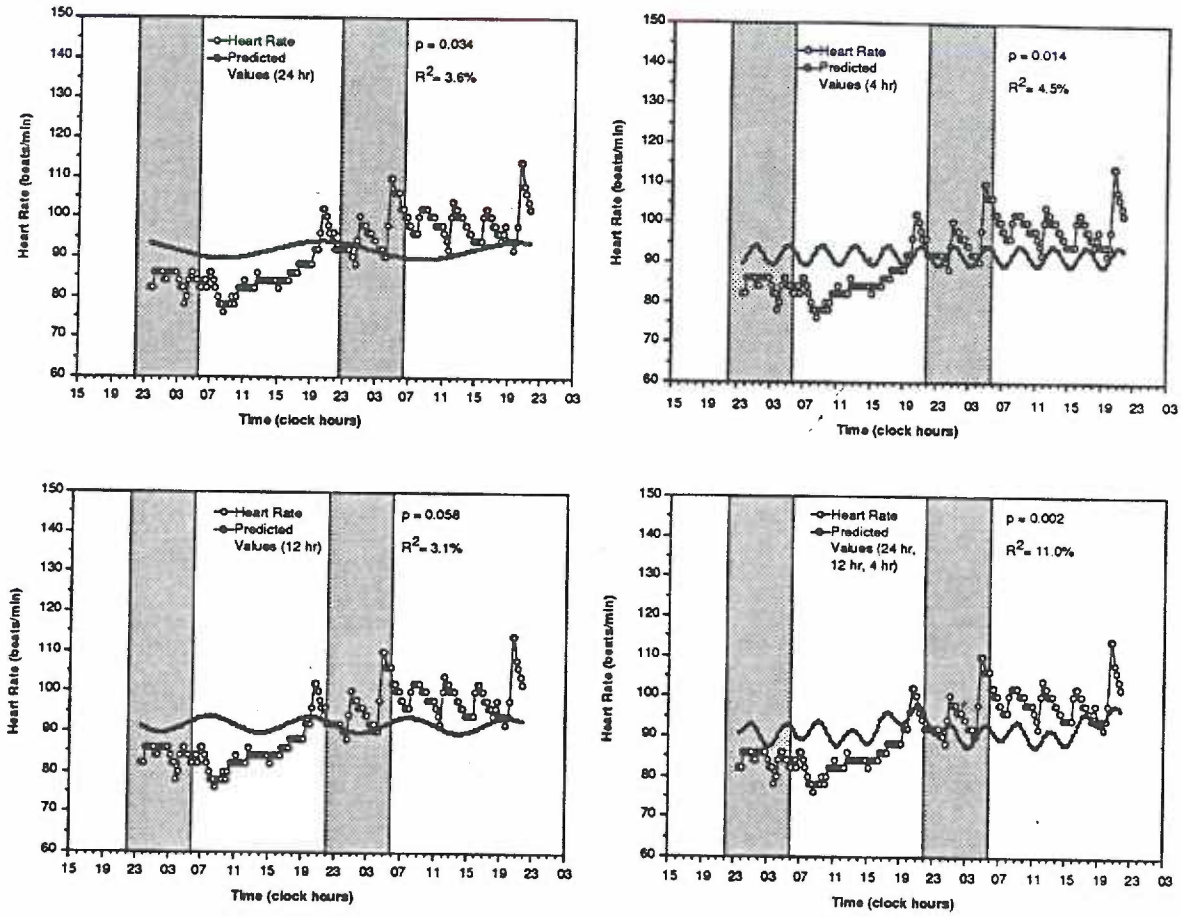


Figure 22. Graphs of 15-minute averaged heart rate data with fitted cosine curves for significant rhythms (24 hr; 12 hr; 4 hr; and 24 hr, 12 hr, and 4 hr) (Subject 1). Customary sleep time is shaded; this was not the sleep time during the study.

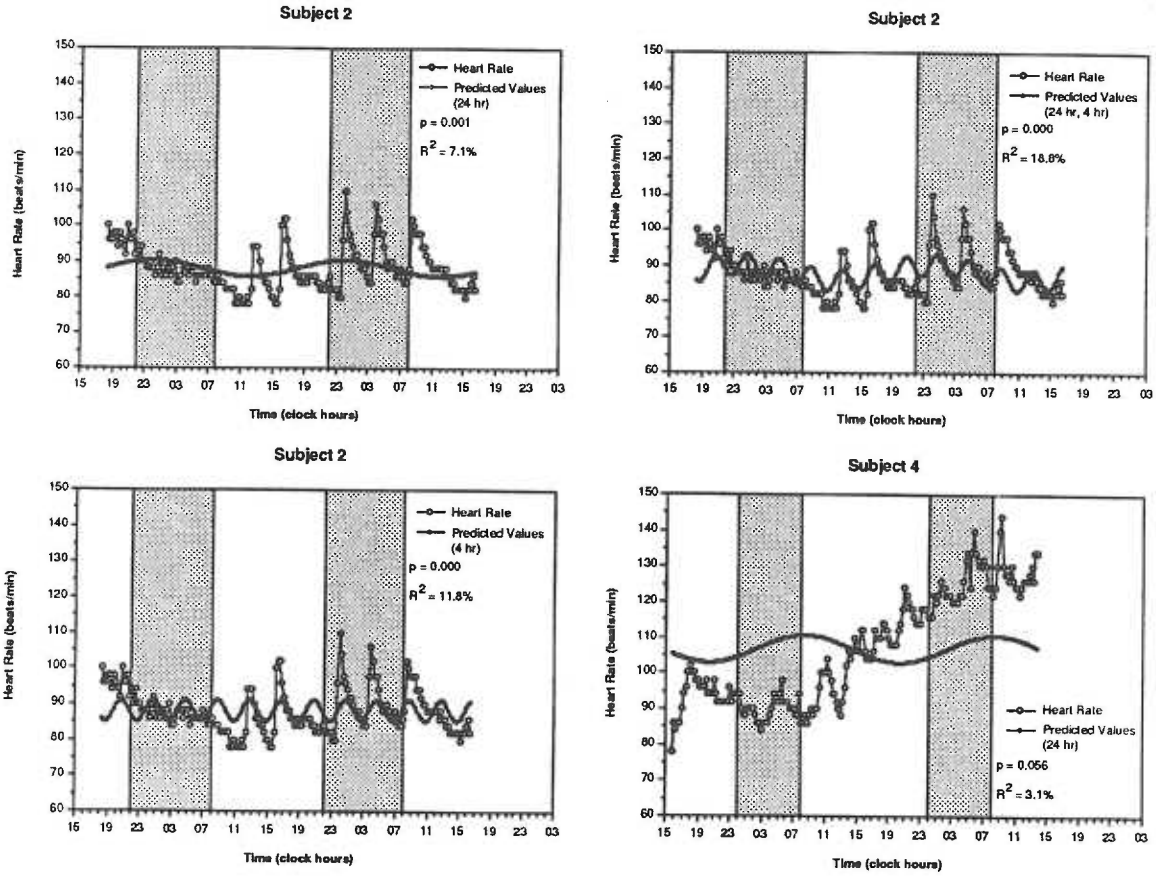


Figure 23. Graphs of 15-minute averaged heart rate data with fitted cosine curve for significant rhythms (Subject 2 - 24 hr; 4 hr; and 24 hr and 4 hr. Subject 4 - 24 hr). Customary sleep time is shaded; this was not the sleep time during the study.

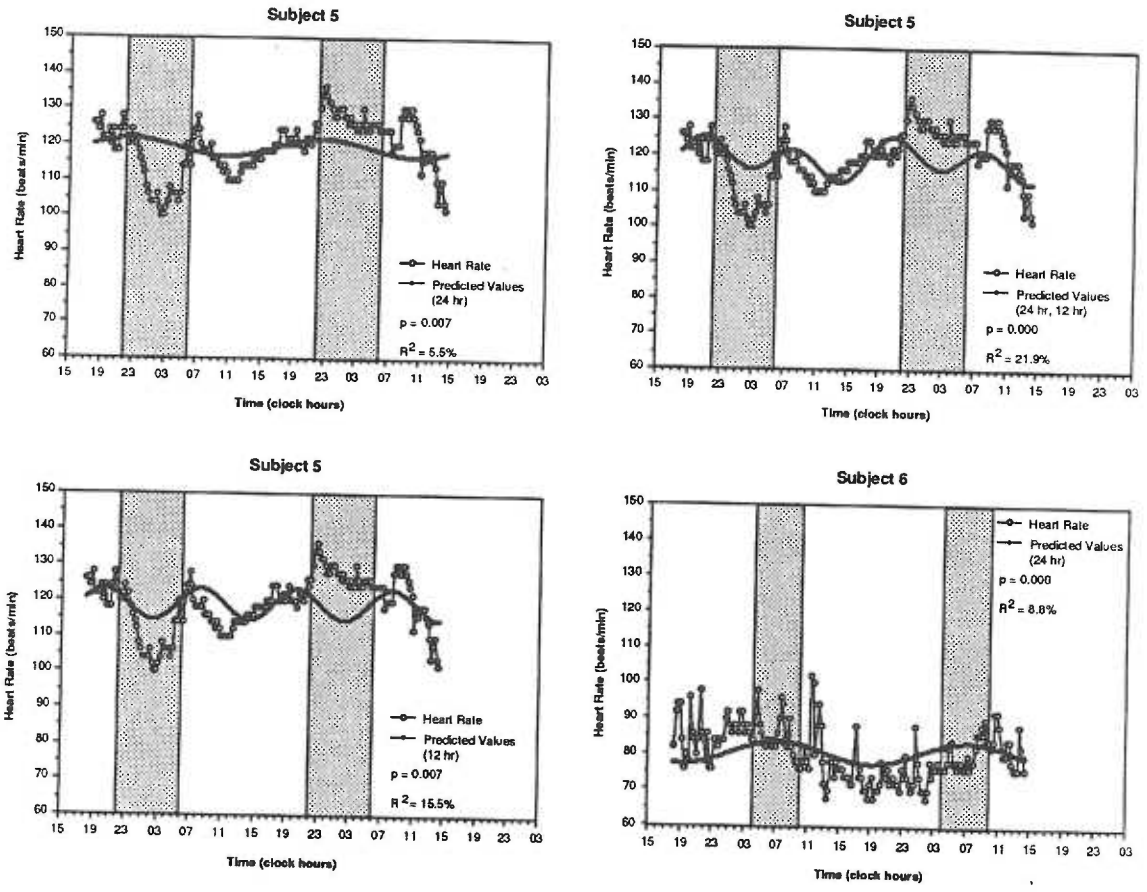


Figure 24. Graphs of 15-minute averaged heart rate data with fitted cosine curves with significant rhythms (Subject 5 - 24 hr; 12 hr; 24 hr and 12 hr; Subject 6 - 24 hr). Customary sleep time is shaded; this was not the sleep time during the study.

Table 16

Criteria Used to Divide Data into Two Segments and Duration of Each Segment

Subject	Criteria	First segment	Second segment
1	Extubation and start of respiratory therapy (day 2, 2005)	20.50 hr	26.00 hr
2	Extubation and start of respiratory therapy (day 2, 1226)	18.25 hr	28.50 hr
3	Extubation (day 2, 1700)	18.25 hr	25.75 hr
4	Extubation and start of respiratory therapy (day 2, 1325)	22.75 hr	24.25 hr
5	Extubation (day 2, 1937)	25.50 hr	18.00 hr
6	Middle of cosine trough used (Extubation not until end of data collection) (day 2, 1900)	24.75 hr	19.50 hr

Table 17

Cosinor Analysis of Heart Rate Data Divided into Two Segments (A and B)

Subject and segment	Period (hr)	Probability	R^2	Mesor ± SE rounded to nearest beat (beats/min)	Half-amplitude (mesor to peak) ± SE rounded to-nearest beat (beats/min)	Acrophase ± SE (clock hr)	Acrophase (hr after customary midsleep)
1A	24	0.000***	53.8%	84 ± 0.3	4 ± 0.3	2047 ± 21 min	18 hr, 47 min ± 21 min
1B	24	0.098+	4.7%	98 ± 0.5	2 ± 0.7	1047 ± 1 hr, 50 min	8 hr, 47 min ± 1 hr, 50 min
1A	12	0.006**	12.6%	84 ± 0.3	2 ± 0.5	0430 ± 32 min	2 hr, 30 min ± 32 min
						1630 ± 32 min	14 hr, 30 min ± 32 min
1B	12	0.007**	9.4%	98 ± 0.5	2 ± 0.7	0713 ± 35 min	5 hr, 13 min ± 35 min
						1913 ± 35 min	17 hr, 13 min ± 35 min
1A	6	0.000***	20.0%	84 ± 0.3	2 ± 0.5	0043 ± 13 min	22 hr, 43 min ± 13 min
						0643 ± 13 min	4 hr, 43 min ± 13 min
						1243 ± 13 min	10 hr, 43 min ± 13 min
						1843 ± 13 min	16 hr, 43 min ± 13 min
1B	6	NS					
1A	4	NS					
1B	4	0.000***	33.3%	98 ± 0.4	4 ± 0.6	0109 ± 5 min	23 hr, 9 min ± 5 min
						0509 ± 5 min	3 hr, 9 min ± 5 min
						0909 ± 5 min	7 hr, 9 min ± 5 min
						1309 ± 5 min	11 hr, 9 min ± 5 min
						1709 ± 5 min	15 hr, 9 min ± 5 min
						2109 ± 5 min	19 hr, 9 min ± 5 min
1A	24,12,6	0.000***	66.9%	84 ± 0.2	3 (24 hr)	2029	18 hr, 29 min
					1 (12 hr)	0501	3 hr, 1 min
						1701	15 hr, 1 min
					2 (6 hr)	0047	22 hr, 47 min
						0647	4 hr, 47 min
						1247	10 hr, 47 min
						1847	16 hr, 47 min

table continues

Table 17 (continued)

Subject and segment	Period (hr)	Probability	R^2	Mesor ± SE rounded to nearest beat (beats/min)	Half-amplitude (mesor to peak) ± SE rounded to nearest beat (beats/min)	Acrophase ± SE (clock hr)	Acrophase (hr after customary midsleep)
1B	24,12,4	0.000***	48.9%	98 ± 0.4	2 (24 hr)	1021	8 hr, 21 min
					2 (12 hr)	0707	5 hr, 7 min
						1907	17 hr, 7 min
					4 (4 hr)	0109	23 hr, 9 min
						0509	3 hr, 9 min
						0909	7 hr, 9 min
						1309	11 hr, 9 min
						1709	15 hr, 9 min
						2109	19 hr, 9 min
2A	24	0.000***	67.0%	88 ± 0.4	6 ± 0.7	2046 ± 26 min	17 hr, 46 min ± 26 min
2B	24	0.000***	15.4%	89 ± 0.6	4 ± 0.8	0536 ± 52 min	2 hr, 36 min ± 52 min
2A	12	0.009**	12.7%	88 ± 0.7	3 ± 0.9	0652 ± 38 min	3 hr, 52 min ± 38 min
						1852 ± 38 min	15 hr, 52 min ± 38 min
2B	12	NS					
2A	6	0.026*	9.9%	88 ± 0.6	2 ± 0.9	0158 ± 20 min	22 hr, 58 min ± 20 min
						0758 ± 20 min	4 hr, 58 min ± 20 min
						1358 ± 20 min	10 hr, 58 min ± 20 min
						1958 ± 20 min	16 hr, 58 min ± 20 min
2B	6	0.014*	7.5%	88 ± 0.6	3 ± 0.8	0524 ± 19 min	2 hr, 24 min ± 19 min
						1124 ± 19 min	8 hr, 24 min ± 19 min
						1724 ± 19 min	14 hr, 24 min ± 19 min
						2324 ± 19 min	20 hr, 24 min ± 19 min

table continues

Table 17 (continued)

Subject and segment	Period (hr)	Probability	R^2	Mesor ± SE rounded to nearest beat (beats/min)	Half-amplitude (mesor to peak) ± SE rounded to nearest beat (beats/min)	Acrophase ± SE (clock hr)	Acrophase (hr after customary midsleep)
2A	4	NS					
2B	4	0.000***	27.4%	88 ± 0.5	5 ± 0.8	0045 ± 6 min	21 hr, 45 min ± 6 min
						0445 ± 6 min	1 hr, 45 min ± 6 min
						0845 ± 6 min	5 hr, 45 min ± 6 min
						1245 ± 6 min	9 hr, 45 min ± 6 min
						1645 ± 6 min	13 hr, 45 min ± 6 min
						2045 ± 6 min	17 hr, 45 min ± 6 min
2A	24,12,6	0.000***	90.8%	88 ± 0.3	6 (24 hr)	2057	17 hr, 57 min
					4 (12 hr)	0631	3 hr, 31 min
						1831	15 hr, 31 min
					1 (6 hr)	0033	21 hr, 33 min
						0633	3 hr, 33 min
						1233	9 hr, 33 min
						1833	15 hr, 33 min
2B	24,6,4	0.000***	47.0%	89 ± 0.5	3 (24 hr)	0542	2 hr, 42 min
					2 (6 hr)	0511	2 hr, 11 min
						1111	8 hr, 11 min
						1711	14 hr, 11 min
						2311	20 hr, 11 min
					5 (4 hr)	0045	21 hr, 45 min
						0445	1 hr, 45 min
						0845	5 hr, 45 min
						1245	9 hr, 45 min
						1645	13 hr, 45 min
						2045	17 hr, 45 min

table continues

Table 17 (continued)

Subject and segment	Period (hr)	Probability	R^2	Mesor ± SE rounded to nearest beat (beats/min)	Half-amplitude (mesor to peak) ± SE rounded to nearest beat (beats/min)	Acrophase ± SE (clock hr)	Acrophase (hr after customary midsleep)
3A	24	0.000***	44.2%	102 ± 0.5	4 ± 0.7	0226 ± 41 min	22 hr, 56 min ± 41 min
3B	24	0.000***	43.5%	105 ± 0.3	4 ± 0.5	1303 ± 25 min	9 hr, 33 min ± 25 min
3A	12	NS					
3B	12	NS					
3A	6	NS					
3B	6	0.036*	6.4%	105 ± 0.4	2 ± 0.6	0455 ± 22 min	1 hr, 25 min ± 22 min
						1055 ± 22 min	7 hr, 25 min ± 22 min
						1655 ± 22 min	13 hr, 25 min ± 22 min
						2255 ± 22 min	19 hr, 25 min ± 22 min
3A	4	NS					
3B	4	NS					
3B	24,6	0.000***	49.0%	105 ± 0.3	4 (24 hr)	1258	9 hr, 28 min
					1 (6 hr)	0452	1 hr, 22 min
						1052	7 hr, 22 min
						1652	13 hr, 22 min
						2252	19 hr, 22 min
4A	24	0.006**	11.6%	92 ± 0.5	2 ± 0.7	1650 ± 1 hr, 7 min	12 hr, 50 min ± 1 hr, 7 min
4B	24	0.000***	56.7%	120 ± 0.7	10 ± 0.9	0638 ± 20 min	2 hr, 38 min ± 20 min
4A	12	0.001***	14.9%	92 ± 0.5	3 ± 0.7	0908 ± 28 min	5 hr, 8 min ± 28 min
						2108 ± 28 min	17 hr, 8 min ± 28 min
4B	12	0.042*	6.5%	120 ± 1.0	4 ± 1.3	0940 ± 44 min	5 hr, 40 min ± 44 min
						2140 ± 44 min	17 hr, 40 min ± 44 min

table continues

Table 17 (continued)

Subject and segment	Period (hr)	Probability	R^2	Mesor ± SE rounded to nearest beat (beats/min)	Half-amplitude (mesor to peak) ± SE rounded to nearest beat (beats/min)	Acrophase ± SE (clock hr)	Acrophase (hr after customary midsleep)
4A	6	0.000***	23.8%	92 ± 0.5	3 ± 0.7	0553 ± 11 min	1 hr, 53 min ± 11 min
						1153 ± 11 min	7 hr, 53 min ± 11 min
						1753 ± 11 min	13 hr, 53 min ± 11 min
						2353 ± 11 min	19 hr, 53 min ± 11 min
4B	6	NS					
4A	4	0.047*	7.0%	92 ± 0.5	2 ± 0.7	0231 ± 15 min	22 hr, 31 min ± 15 min
						0631 ± 15 min	2 hr, 31 min ± 15 min
						1031 ± 15 min	6 hr, 31 min ± 15 min
						1431 ± 15 min	10 hr, 31 min ± 15 min
						1831 ± 15 min	14 hr, 31 min ± 15 min
						2231 ± 15 min	18 hr, 31 min ± 15 min
4B	4	0.072+	5.4%	120 ± 1.0	3 ± 1.4	0124 ± 17 min	21 hr, 24 min ± 17 min
						0524 ± 17 min	1 hr, 24 min ± 17 min
						0924 ± 17 min	5 hr, 24 min ± 17 min
						1324 ± 17 min	9 hr, 24 min ± 17 min
						1724 ± 17 min	13 hr, 24 min ± 17 min
						2124 ± 17 min	17 hr, 24 min ± 17 min

table continues

Table 17 (continued)

Subject and segment	Period (hr)	Probability	R^2	Mesor ± SE rounded to nearest beat (beats/min)	Half-amplitude (mesor to peak) ± SE rounded to nearest beat (beats/min)	Acrophase ± SE (clock hr)	Acrophase (hr after customary midsleep)
4A	24,12,6,4	0.000***	53.4%	92 ± 0.4	2 (24 hr)	1834	14 hr, 34 min
					3 (12 hr)	0909	5 hr, 9 min
						2109	17 hr, 9 min
					4 (6 hr)	0552	1 hr, 52 min
						1152	7 hr, 52 min
						1752	13 hr, 52 min
						2352	19 hr, 52 min
					1 (4 hr)	0227	22 hr, 27 min
						0627	2 hr, 27 min
						1027	6 hr, 27 min
						1427	10 hr, 27 min
						1827	14 hr, 27 min
						2227	18 hr, 27 min
4B	24,12,4	0.000***	68.9%	120 ± 0.6	10 (24 hr)	0637	2 hr, 37 min
					3 (12 hr)	0212	22 hr, 12 min
						1412	10 hr, 12 min
					3 (4 hr)	0124	21 hr, 24 min
						0524	1 hr, 24 min
						0924	5 hr, 24 min
						1324	9 hr, 24 min
						1724	13 hr, 24 min
						2124	17 hr, 24 min

table continues

Table 17 (continued)

Subject and segment	Period (hr)	Probability	R^2	Mesor ± SE rounded to nearest beat (beats/min)	Half-amplitude (mesor to peak) ± SE rounded to nearest beat (beats/min)	Acrophase ± SE (clock hr)	Acrophase (hr after customary midsleep)
5A	24	0.000***	29.9%	116 ± 0.6	5 ± 0.8	1727 ± 37 min	15 hr, 27 min ± 37 min
5B	24	0.000***	50.3%	122 ± 0.6	8 ± 0.8	0233 ± 26 min	33 min ± 26 min
5A	12	0.000***	46.3%	116 ± 0.5	6 ± 0.7	0747 ± 13 min	5 hr, 47 min ± 13 min
						1947 ± 13 min	17 hr, 47 min ± 13 min
5B	12	NS					
5A	6	NS					
5B	6	0.001***	18.2%	123 ± 0.7	4 ± 1.0	0431 ± 15 min	2 hr, 31 min ± 15 min
						1031 ± 15 min	8 hr, 31 min ± 15 min
						1631 ± 15 min	14 hr, 31 min ± 15 min
						2231 ± 15 min	20 hr, 31 min ± 15 min
5A	4	NS					
5B	4	NS					
5A	24,12	0.000***	69.8%	115 ± 0.4	5 (24 hr)	1715	15 hr, 15 min
					6 (12 hr)	0751	5 hr, 51 min
						1951	17 hr, 51 min
5B	24,6	0.000***	61.6%	122 ± 0.6	7 (24 hr)	0229	29 min
					3 (6 hr)	0435	2 hr, 35 min
						1035	8 hr, 35 min
						1635	14 hr, 35 min
						2235	18 hr, 35 min

table continues

Table 17 (continued)

Subject and segment	Period (hr)	Probability	R^2	Mesor ± SE rounded to nearest beat (beats/min)	Half-amplitude (mesor to peak) ± SE rounded to nearest beat (beats/min)	Acrophase ± SE (clock hr)	Acrophase (hr after customary midsleep)
6A	24	0.000***	22.8%	83 ± 0.7	5 ± 0.9	0339 ± 43 min	20 hr, 39 min ± 43 min
6B	24	0.000***	51.4%	78 ± 0.5	5 ± 0.7	1029 ± 32 min	3 hr, 29 min ± 32 min
6A	12	NS					
6B	12	NS					
6A	6	NS					
6B	6	0.079+	6.1%	78 ± 0.6	2 ± 0.9	0437 ± 26 min	21 hr, 37 min ± 26 min
						1037 ± 26 min	3 hr, 37 min ± 26 min
						1637 ± 26 min	9 hr, 37 min ± 26 min
						2237 ± 26 min	15 hr, 37 min ± 26 min
6A	4	0.050*	6.1%	83 ± 0.7	3 ± 1.0	0013 ± 16 min	17 hr, 13 min ± 16 min
						0413 ± 16 min	21 hr, 13 min ± 16 min
						0813 ± 16 min	1 hr, 13 min ± 16 min
						1213 ± 16 min	5 hr, 13 min ± 16 min
						1613 ± 16 min	9 hr, 13 min ± 16 min
						2013 ± 16 min	13 hr, 13 min ± 16 min
6B	4	NS					

table continues

Table 17 (continued)

Subject and segment	Period (hr)	Probability	R^2	Mesor ± SE rounded to nearest beat (beats/min)	Half-amplitude (mesor to peak) ± SE rounded to nearest beat (beats/min)	Acrophase ± SE (clock hr)	Acrophase (hr after customary midsleep)
6A	24,4	0.000***	28.0%	83 ± 0.7	5 (24 hr) 2 (4 hr)	0335 0010 0410 0810 1210 1610 2010	20 hr, 35 min 17 hr, 10 min 21 hr, 10 min 1 hr, 10 min 5 hr, 10 min 9 hr, 10 min 13 hr. 10 min
6B	24,6	0.000***	58.7%	78 ± 0.5	5 (24 hr) 2 (6 hr)	1051 0422 1022 1622 2222	3 hr, 51 min 21 hr, 22 min 3 hr, 22 min 9 hr, 22 min 15 hr, 22 min

NS = nonsignificant + = $p \leq 0.10$ (trend) * = $p \leq 0.05$ ** = $p \leq 0.01$ *** = $p \leq 0.001$

found in Segment A only. Subject 3 had no 12-hour rhythms. In Subject 4, 12-hour rhythms were found in Segments A and B separately but not when data were analyzed as a whole. In Subject 5, 12-hour rhythms were found in the whole data set and in Segment A. Subject 6 had no 12-hour rhythms.

No 6-hour rhythms were found in the data as a whole but were found in Segment A only ($\underline{n}$=2), Segment B only ($\underline{n}$=3), or both segments ($\underline{n}$=1).

Four-hour rhythms were not found in the whole data set for Subjects 3, 4, 5, and 6, but were found in Segment A only (Subject 6) or in both segments (Subject 4). Subjects 1 and 2 had significant 4-hour rhythms in the whole data set and in Segment B, but not in Segment A. Respiratory therapy was given only in Segment B and contributed to the 4-hour rhythmicity found in these two subjects.

Explained variance (R^2) increased considerably (R^2 in both segments ranged 4.7%-90.8%) when segments were analyzed separately and differed between segments. Explained variances (R^2) in heart rate for the significant 24-hour rhythms are listed for Segments A and B for each subject:

Subject	Segment A	Segment B
1	53.8%	4.7%
2	67.0%	15.4%
3	44.2%	43.5%
4	11.6%	56.7%
5	29.9%	50.3%
6	22.8%	51.4%

Mesors, amplitudes, and acrophases were also different between Segments A and B. Within Segment A, acrophases (expressed as hours after customary midsleep) for 24-hour rhythm were nonoverlapping and generally occurred later than expected. Within Segment B, acrophases

were more similar and occurred earlier than expected. In Segment B, acrophases of Subjects 2, 4, and 6 overlapped and acrophases for Subjects 1 and 3 overlapped. Acrophases for the 24-hour rhythms in heart rate for each segment are as follows:

Subject	Segment A	Segment B
1	18 hr, 47 min ± 21 min	8 hr, 47 min ± 1 hr, 50 min
2	17 hr, 46 min ± 26 min	2 hr, 36 min ± 52 min
3	22 hr, 56 min ± 41 min	9 hr, 33 min ± 25 min
4	12 hr, 50 min ± 1 hr, 7 min	2 hr, 38 min ± 20 min
5	15 hr, 27 min ± 37 min	33 min ± 26 min
6	20 hr, 39 min ± 43 min	3 hr, 29 min ± 32 min

When comparing the 24-hour-rhythm acrophases in the divided analysis with acrophases in the whole data set, only in two cases were they similar. In Subject 1, the acrophase in Segment A overlapped with the acrophase in the whole data set; and in Subject 4, the acrophase in Segment B overlapped with acrophase in the whole data set.

Acrophases for the 12-hour rhythms in heart rate for each segment are as follows:

Subject	Segment A	Segment B
1	2 hr, 30 min ± 32 min	5 hr, 13 min ± 35 min
2	3 hr, 52 min ± 38 min	
4	5 hr, 8 min ± 28 min	5 hr, 40 min ± 44 min
5	5 hr, 47 min ± 13 min	

Within Segment A, 12-hour-rhythm acrophases overlapped in Subjects 4 and 5; in Segment B overlap was found between Subjects 1 and 4. When comparing the 12-hour acrophases in the divided data set with acrophases in the whole data set, agreement varied. For Subject 1, acrophases were overlapping between the whole data set and Segment B. For Subject 5, acrophases in the whole data set overlapped with acrophases in Segment A.

Acrophases for the 6-hour rhythms in heart rate are as follows:

Subject	Segment A	Segment B
1	4 hr, 43 min ± 13 min	
2	4 hr, 58 min ± 20 min	2 hr, 24 min ± 19 min
3		1 hr, 25 min ± 22 min
4	1 hr, 53 min ± 11 min	
5		2 hr, 31 min ± 15 min
6		3 hr, 37 min ± 26 min

Acrophases for the 6-hour rhythms within Segment A overlapped in Subjects 1 and 2; acrophases within Segment B overlapped in Subjects 2 and 5. Between segments, acrophases in Subject 2 did not overlap.

Acrophases for the 4-hour rhythms in heart rate for each sequence are as follows:

Subject	Segment A	Segment B
1		3 hr, 9 min ± 5 min
2		1 hr, 45 min ± 6 min
4	2 hr, 31 min ± 15 min	1 hr, 24 min ± 17 min
6	1 hr, 13 min ± 16 min	

In Segment A, acrophases for the 4-hour rhythms did not overlap. In Segment B, Subject 2 and 4 had overlapping acrophases. Acrophases in the whole data set overlapped with acrophases in Segment B (Subjects 1 and 2).

Figures 25-33 illustrate heart rate graphs with fitted cosine curves for Segments A and B for each subject.

First 24 Hour Data Set Analysis

Because splitting the data based on time of extubation did not always allow for a complete 24 hours of data in each analysis, cosinor analysis was repeated on the first 24 hours of heart rate data for each subject (Table 18). In general, findings were similar to those from the analysis of Segment A. Some of the significant rhythms found in Segment

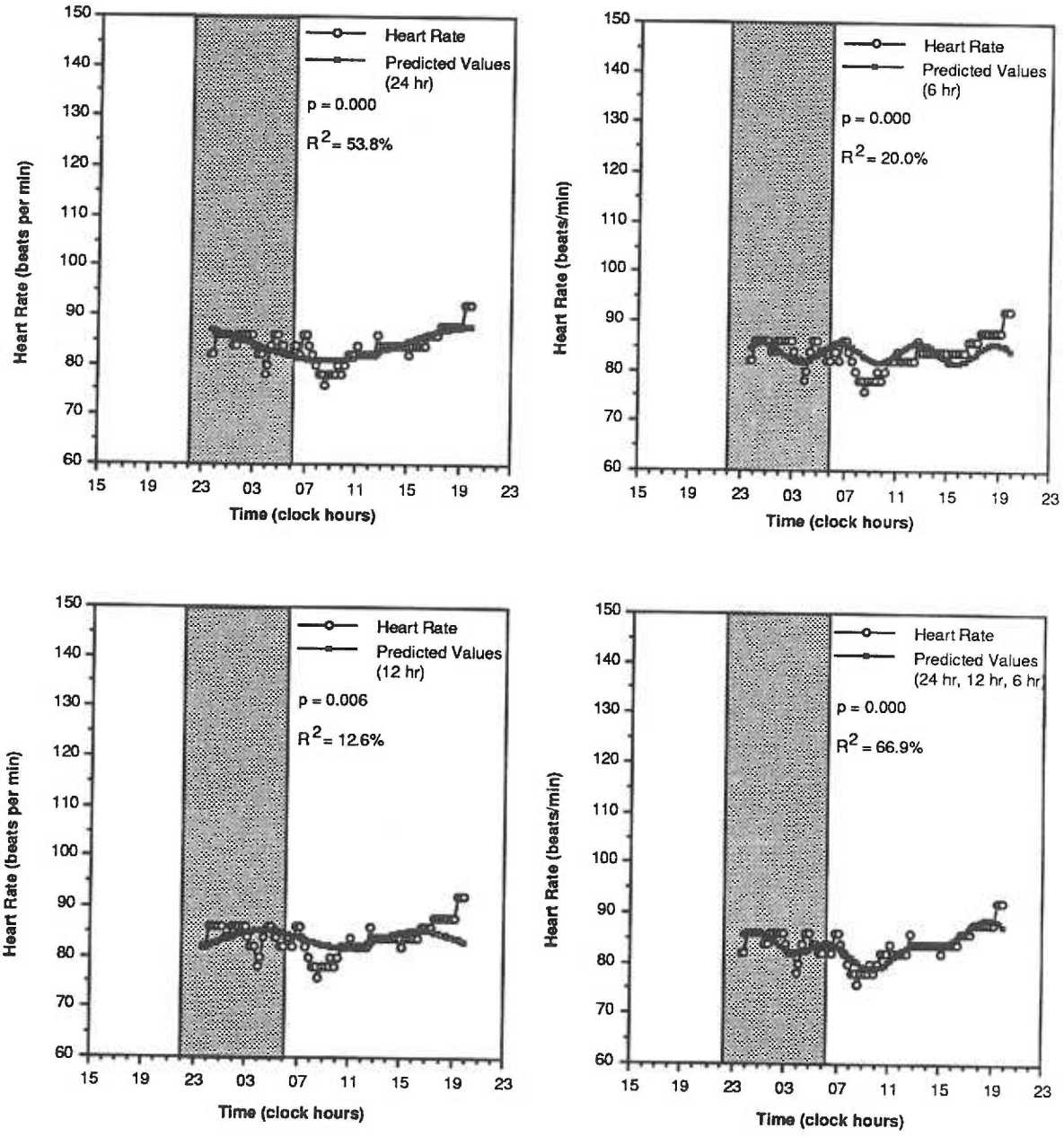


Figure 25. Graphs of 15-minute averaged heart rate data with fitted cosine curves for significant rhythms (24 hr; 12 hr; 6 hr; and 24 hr, 12 hr, and 6 hr) in Segment A (Subject 1). Customary sleep time is shaded; this was not the sleep time during the study.

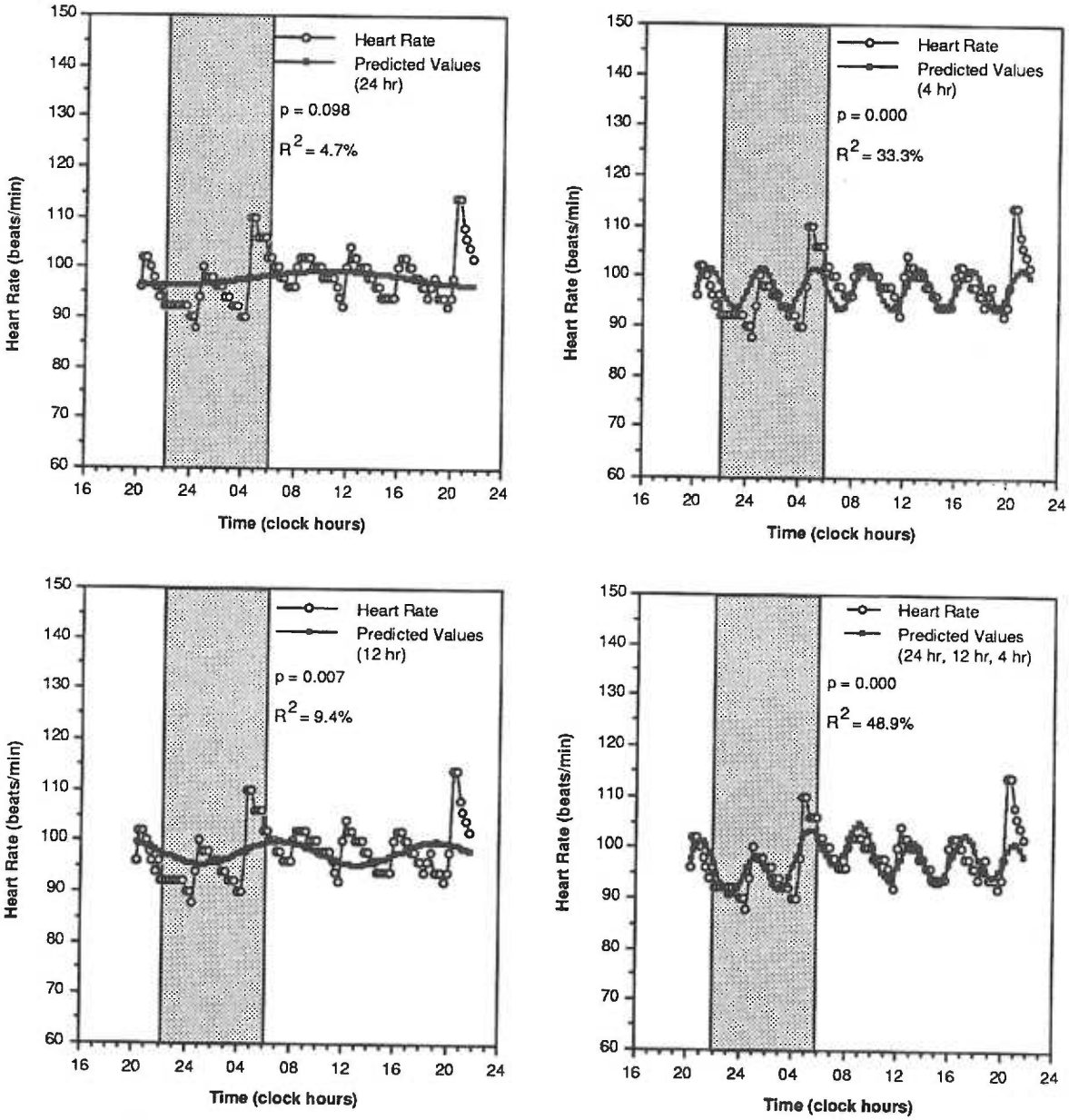


Figure 26. Graphs of 15-minute averaged heart rate data with fitted cosine curves for significant rhythms (24 hr; 12 hr; 4 hr; and 24 hr, 12 hr, and 4 hr) in Segment B (Subject 1). Customary sleep time is shaded; this was not the sleep time during the study.

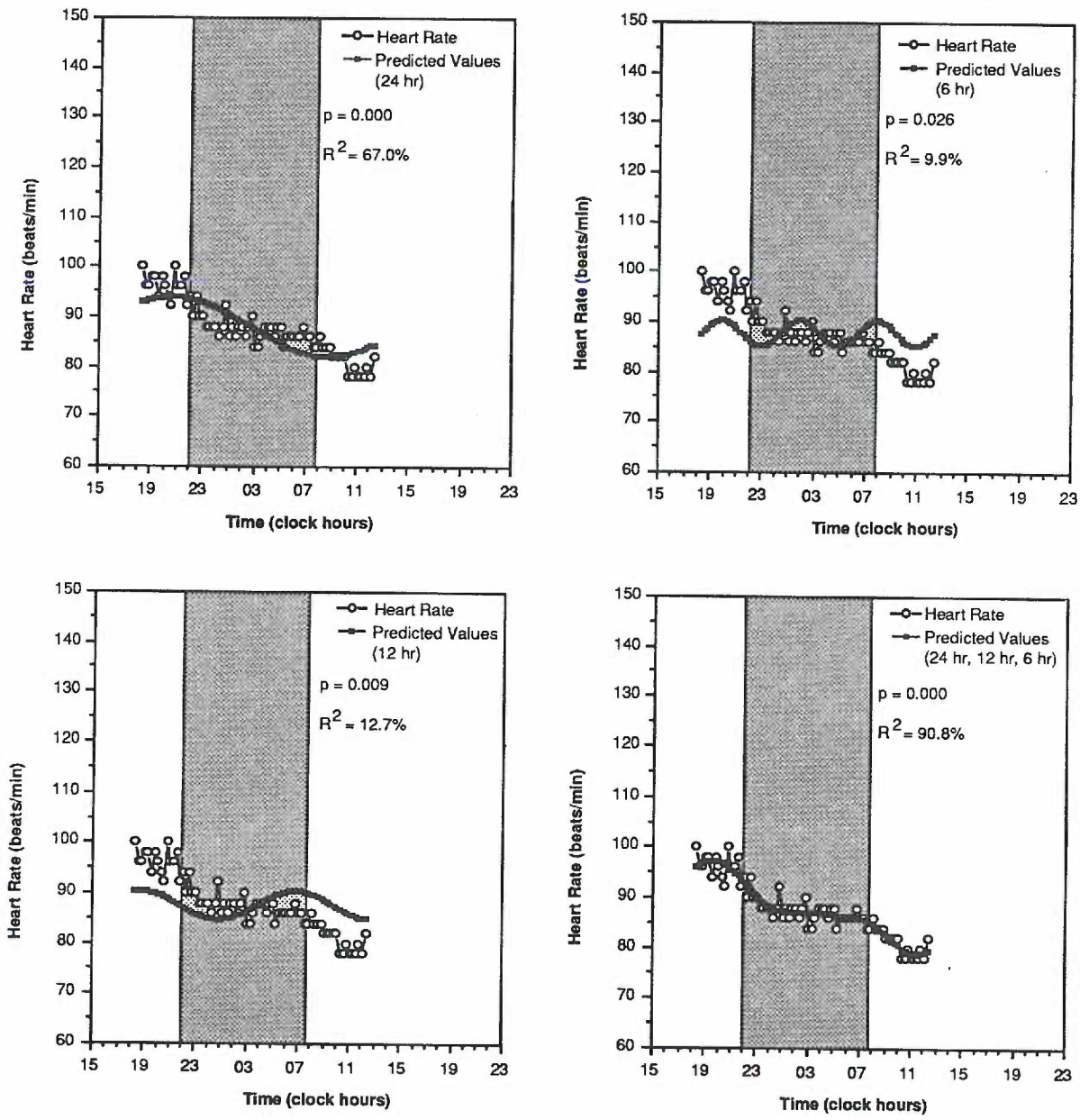


Figure 27. Graphs of 15-minute averaged heart rate data with fitted cosine curves for significant rhythms (24 hr; 12 hr; 6 hr; and 24 hr, 12 hr, and 6 hr) in Segment A (Subject 2). Customary sleep time is shaded; this was not the sleep time during the study.

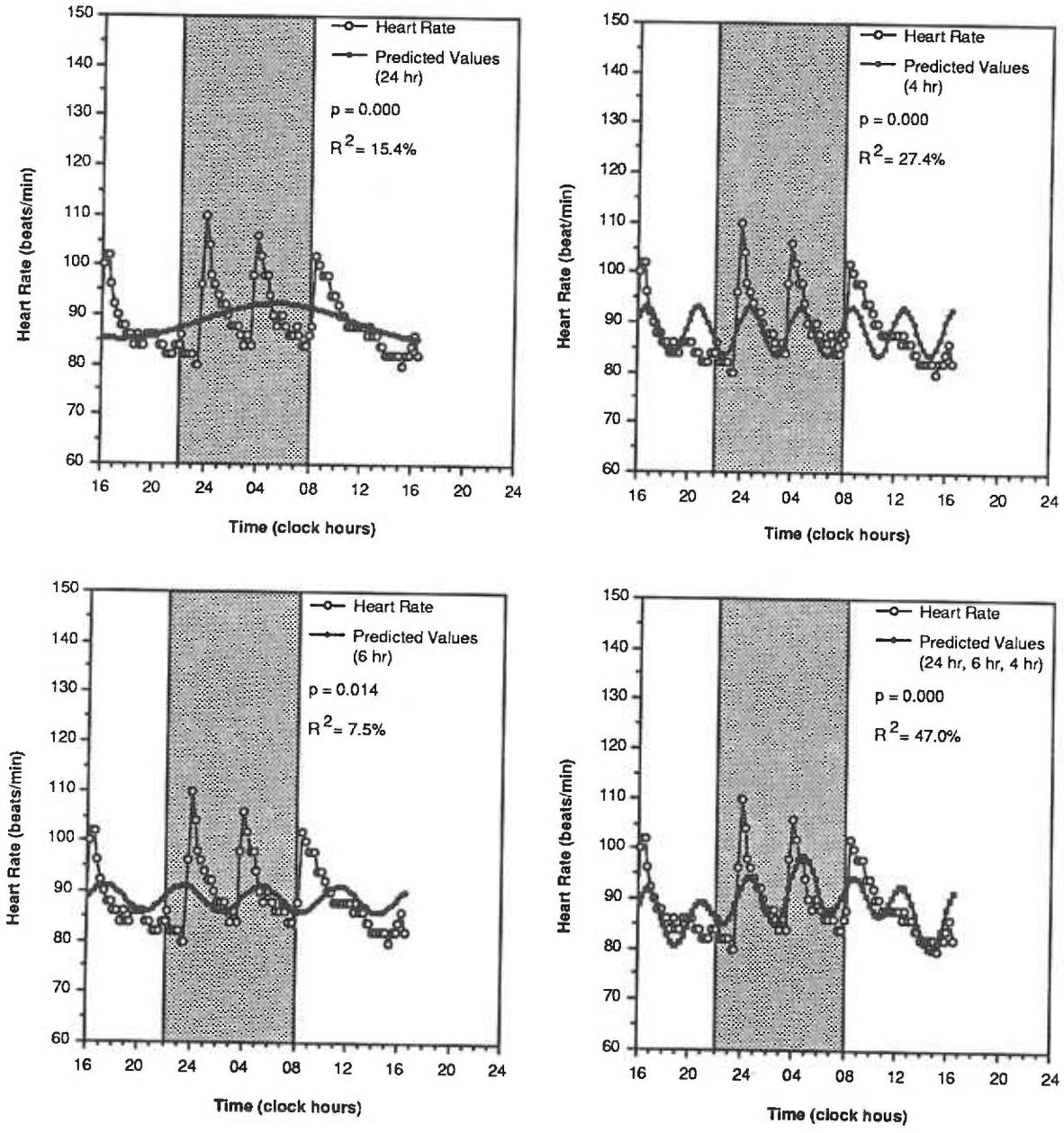


Figure 28. Graphs of 15-minute averaged heart rate data with fitted cosine curves for significant rhythms (24 hr; 6 hr; 4 hr; and 24 hr, 6 hr, and 4 hr) in Segment B (Subject 2). Customary sleep time is shaded; this was not the sleep time during the study.

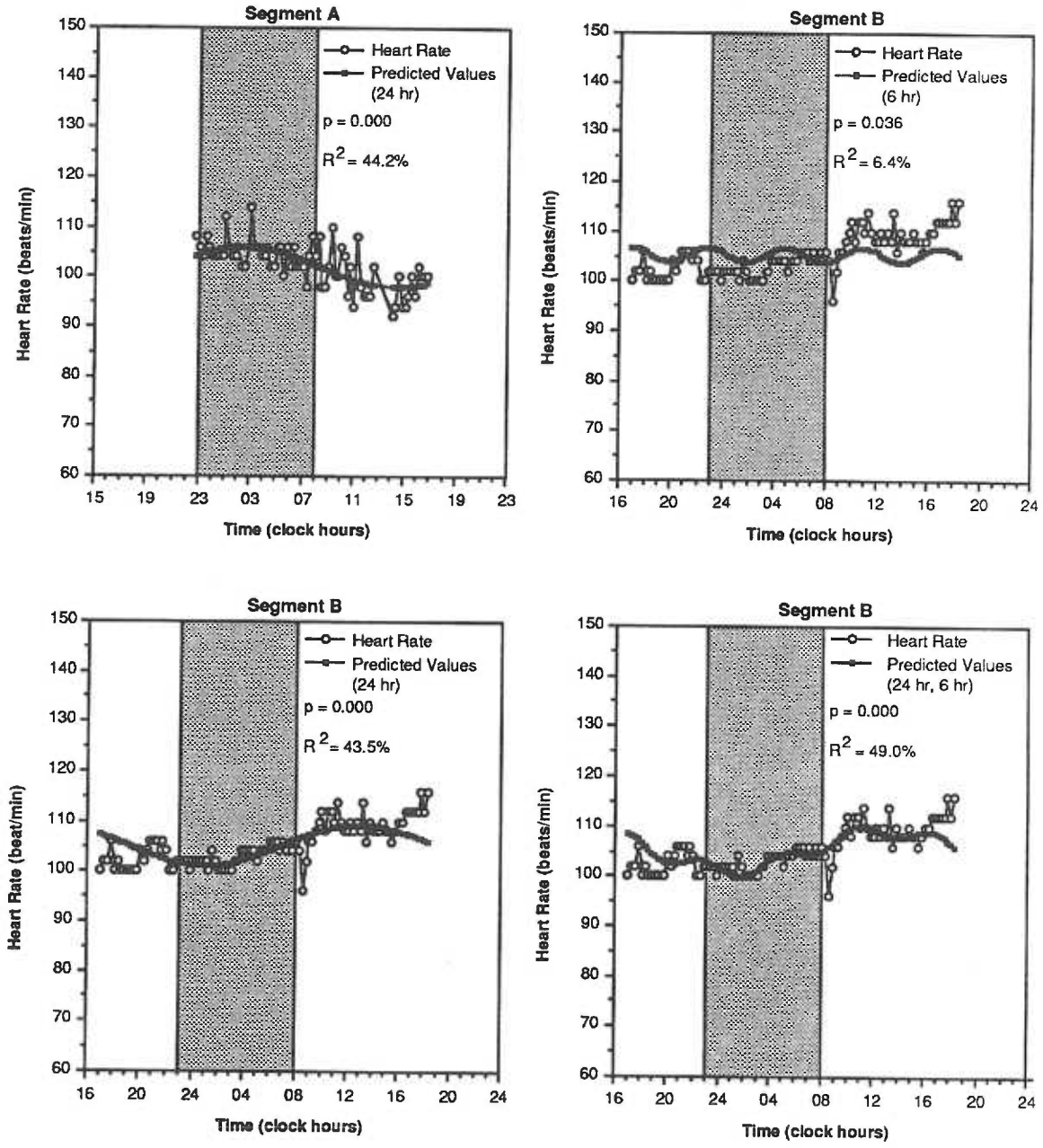


Figure 29. Graphs of 15-minute averaged heart rate data with fitted cosine curves for significant rhythms in Segment A (24 hr) and in Segment B (24 hr; 6 hr; and 24 hr and 6 hr) (Subject 3). Customary sleep time is shaded; this was not the sleep time during the study.

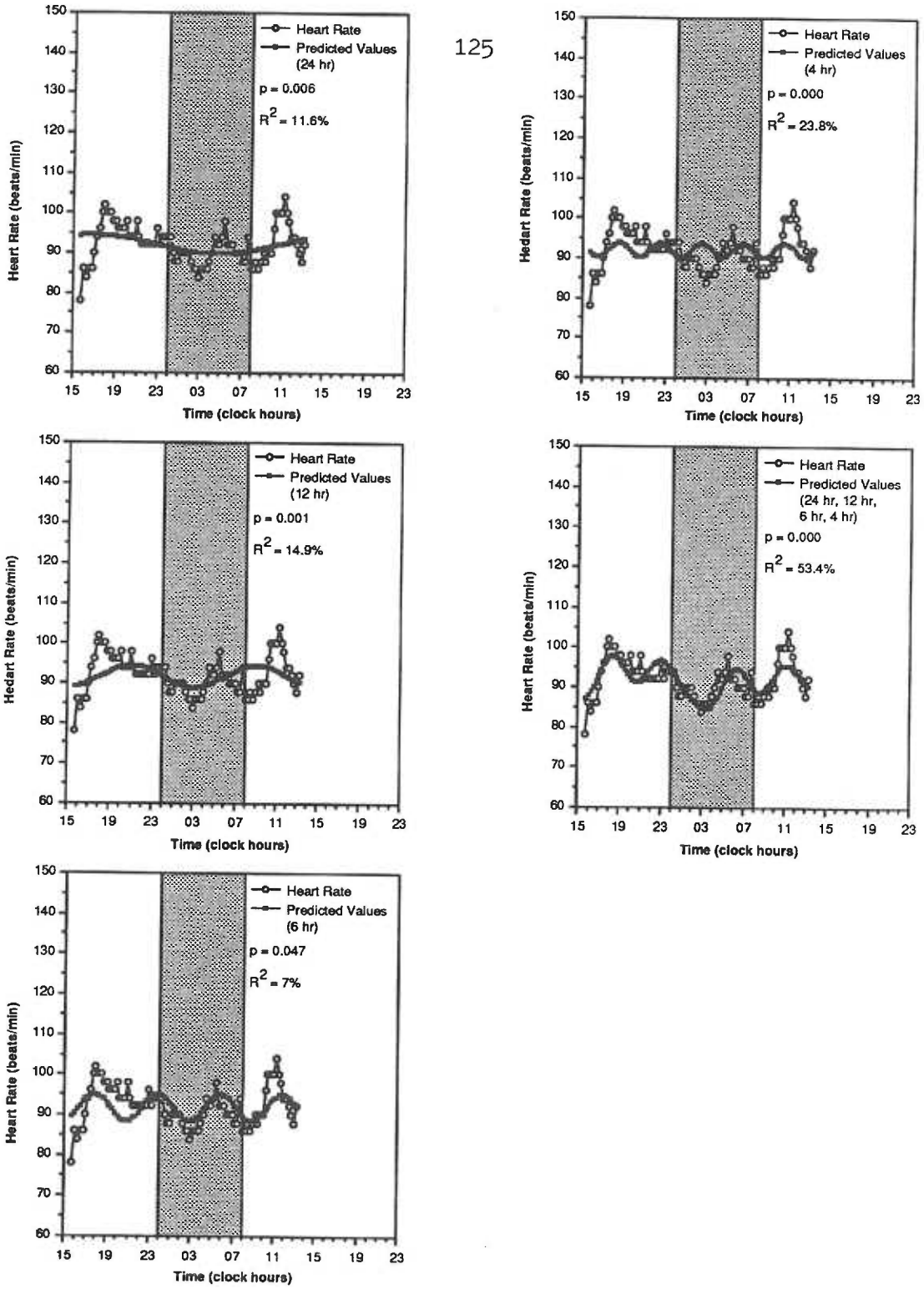


Figure 30. Graphs of 15-minute averaged heart rate data with fitted cosine curves for significant rhythms (24 hr; 12 hr; 4 hr; 6 hr; and 24 hr, 12 hr, 6 hr, and 4 hr) in Segment A (Subject 4). Customary sleep time is shaded; this was not the sleep time during the study.

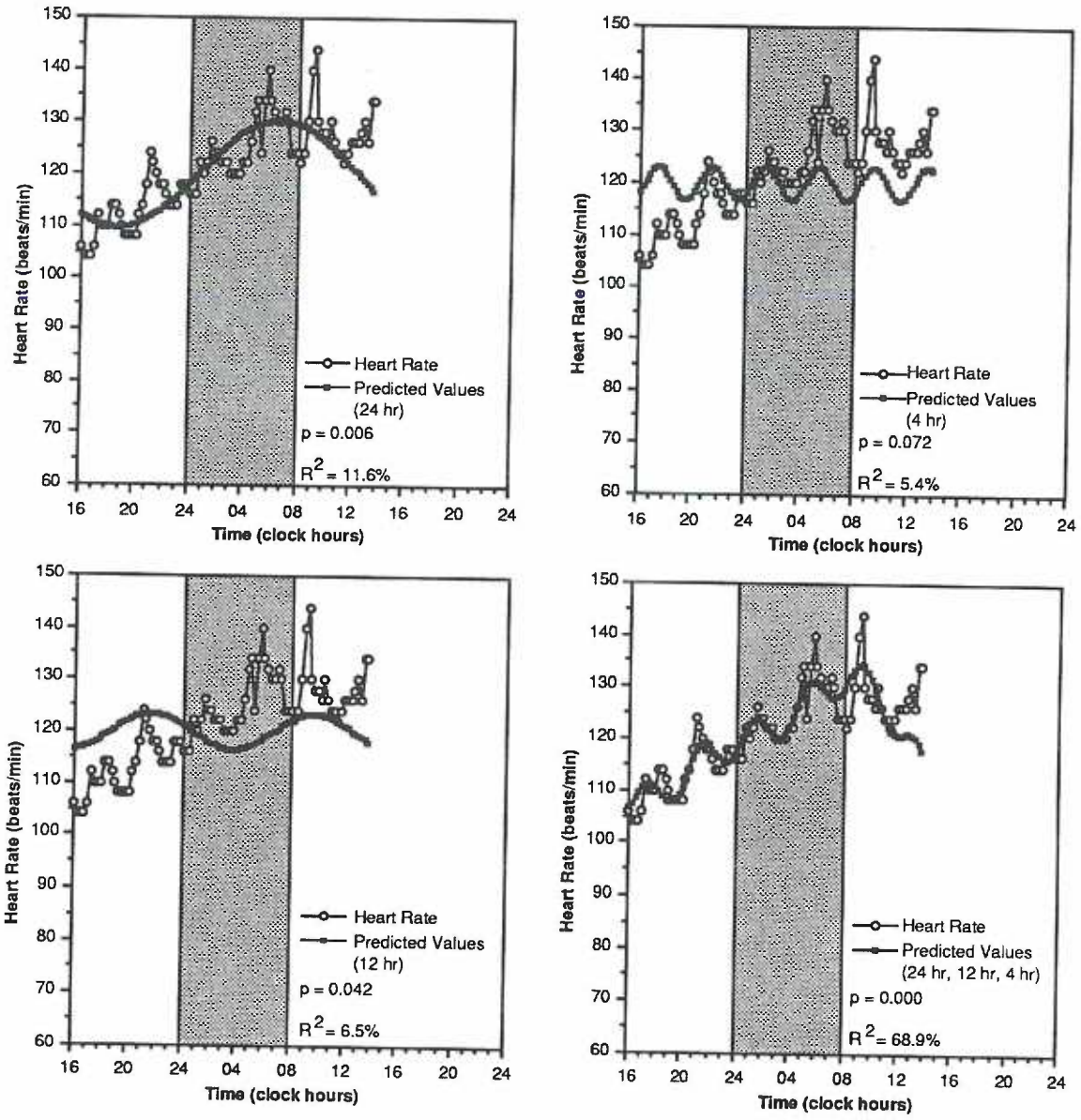


Figure 31. Graphs of 15-minute averaged heart rate data with fitted cosine curves for significant rhythms (24 hr; 12 hr; 4 hr; and 24 hr, 12 hr, and 4 hr) in Segment B (Subject 4). Customary sleep time is shaded; this was not the sleep time during the study.

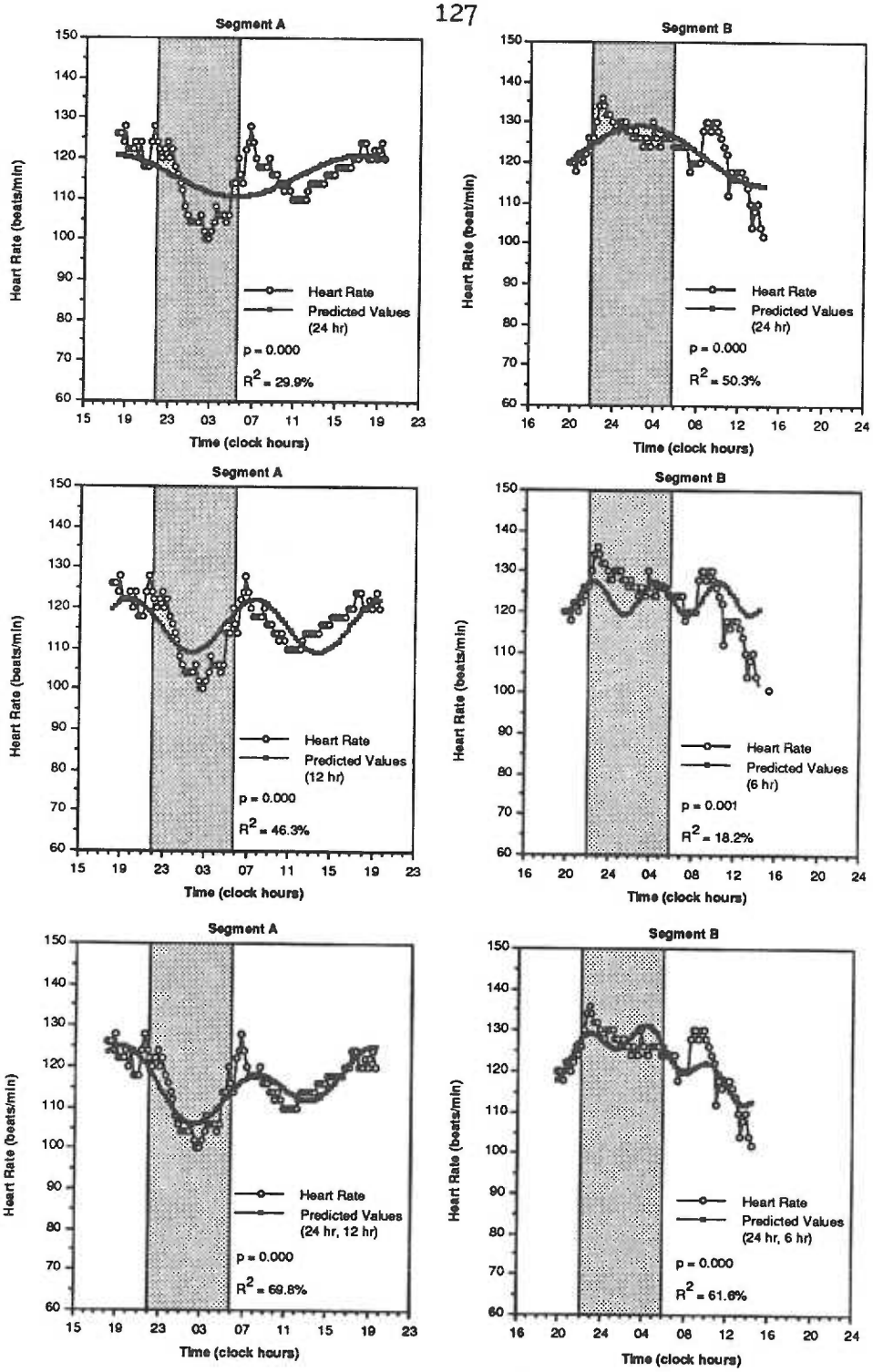


Figure 32. Graphs of 15-minute averaged heart rate data with fitted cosine curves for significant rhythms in Segment A (24 hr; 12 hr; and 24 hr and 12 hr) and in Segment B (24 hr; 6 hr; and 24 hr and 6 hr) (Subject 5). Customary sleep time is shaded; this was not the sleep time during the study.

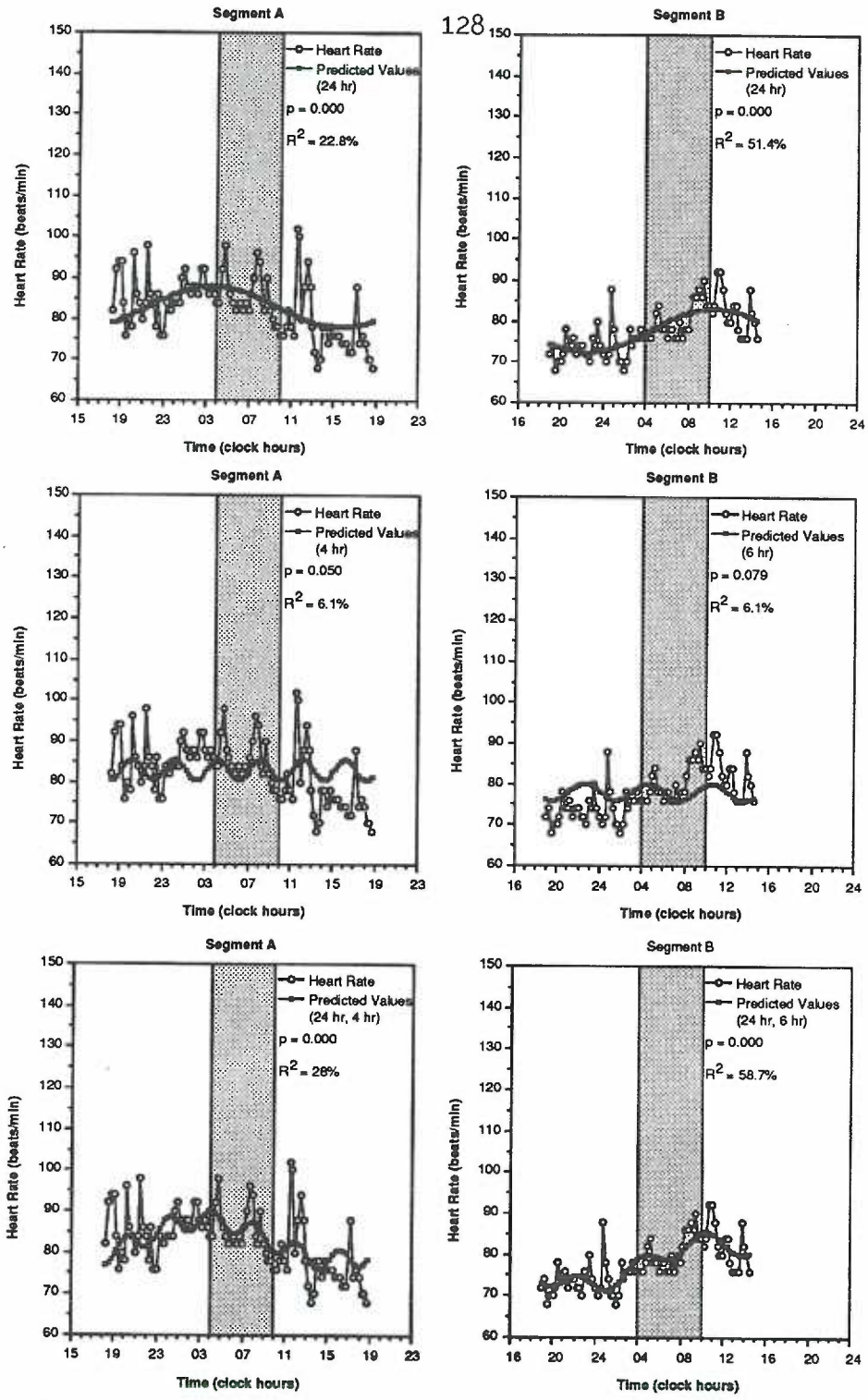


Figure 33. Graphs of 15-minute averaged heart rate data with fitted cosine curves with significant rhythms in Segment A (24 hr; 4 hr; and 24 hr and 4 hr) and in Segment B (24 hr; 6 hr; and 24 hr and 6 hr) (Subject 6). Customary sleep time is shaded; this was not the sleep time during the study.

Table 18

Cosinor Analysis of First 24 Hours of Heart Rate Data

Subject	Period (hr)	Probability	R^2	Mesor ± SE rounded to nearest beat (beats/min)	Half-amplitude (mesor to peak) ± SE rounded to nearest beat (beats/min)	Acrophase ± SE (clock hr)	Acrophase (hr after customary midsleep)
1	24	0.000***	62.0%	86 ± 0.5	6 ± 0.5	2102 ± 19 min	19 hr, 2 min ± 19 min
	12	0.019*	8.0%	86 ± 0.6	2 ± 0.7	0859 ± 40 min	6 hr, 59 min ± 40 min
						2059 ± 40 min	18 hr, 59 min ± 40 min
	6	NS					
	4	NS					
	24,12	0.000***	69.4%	86 ± 0.3	6 (24 hr)	2102	19 hr, 2 min
					2 (12 hr)	0851	6 hr, 51 min
						2051	18 hr, 51 min
2	24	0.000***	41.0%	88 ± 0.5	5 ± 0.7	2059 ± 28 min	17 hr, 59 min ± 28 min
	12	0.021*	7.9%	88 ± 0.6	2 ± 0.8	0648 ± 41 min	3 hr, 48 min ± 41 min
						1848 ± 41 min	15 hr, 48 min ± 41 min
	6	NS					
	4	0.036*	6.8%	88 ± 0.6	2 ± 0.9	0052 ± 15 min	21 hr, 52 min ± 15 min
						0452 ± 15 min	1 hr, 52 min ± 15 min
						0852 ± 15 min	5 hr, 52 min ± 15 min
						1252 ± 15 min	9 hr, 52 min ± 15 min
						1652 ± 15 min	13 hr, 52 min ± 15 min
						2052 ± 15 min	19 hr, 52 min ± 15 min

table continues

Table 18 (continued)

Subject	Period (hr)	Probability	R^2	Mesor ± SE rounded to nearest beat (beats/min)	Half-amplitude (mesor to peak) ± SE rounded to nearest beat (beats/min)	Acrophase ± SE (clock hr)	Acrophase (hr after customary midsleep)
2	24,12,4	0.000***	55.7%	88 ± 0.4	5 (24 hr)	2100	18 hr
					2 (12 hr)	0650	3 hr, 50 min
						1850	15 hr, 50 min
					2 (4 hr)	0051	21 hr, 51 min
						0451	1 hr, 51 min
						0851	5 hr, 51 min
						1251	9 hr, 51 min
						1651	13 hr, 51 min
						2051	17 hr, 51 min
3	24	0.000***	41.4%	102 ± 0.4	4 ± 0.5	0159 ± 30 min	22 hr, 29 min ± 30 min
	12	NS					
	6	NS					
	4	NS					
4	24	0.000***	25.9%	93 ± 0.6	5 ± 0.8	1550 ± 4 min	11 hr, 50 min ± 4 min
	12	NS					
	6	NS					
	4	0.003**	11.4%	94 ± 0.6	3 ± 0.9	0242 ± 11 min	22 hr, 42 min ± 11 min
						0642 ± 11 min	2 hr, 42 min ± 11 min
						1042 ± 11 min	6 hr, 42 min ± 11 min
						1442 ± 11 min	10 hr, 42 min ± 11 min
						1842 ± 11 min	14 hr, 42 min ± 11 min
						2242 ± 11 min	18 hr, 42 min ± 11 min
	24,4	0.000***	37.4%	93 ± 0.5	5 (24 hr)	1550	11 hr, 50 min
					3 (4 hr)	0242	22 hr, 42 min
						0642	2 hr, 42 min
						1042	6 hr, 42 min
						1442	10 hr, 42 min
						1842	14 hr, 42 min
						2242	18 hr, 42 min

table continues

Table 18 (continued)

Subject	Period (hr)	Probability	R^2	Mesor ± SE rounded to nearest beat (beats/min)	Half-amplitude (mesor to peak) ± SE rounded to nearest beat (beats/min)	Acrophase ± SE (clock hr)	Acrophase (hr after customary midsleep)
5	24	0.000***	27.4%	116 ± 0.6	5 ± 0.9	1724 ± 39 min	15 hr, 24 min ± 39 min
	12	0.000***	44.3%	116 ± 0.5	6 ± 0.8	0747 ± 13 min	5 hr, 47 min ± 13 min
						1947 ± 13 min	17 hr, 47 min ± 13 min
	6	NS					
	4	NS					
	24,12	0.000***	70.8%	116 ± 0.4	5 (24 hr)	1724	15 hr, 24 min
					6 (12 hr)	0748	5 hr, 48 min
						1948	17 hr, 48 min
6	24	0.000***	21.3%	83 ± 0.7	5 ± 0.9	0324 ± 45 min	20 hr, 24 min ± 45 min
	12	NS					
	6	NS					
	4	0.098+	4.9%	83 ± 0.7	2 ± 1.0	0007 ± 18 min	17 hr, 7 min ± 18 min
						0407 ± 18 min	21 hr, 7 min ± 18 min
						0807 ± 18 min	1 hr, 7 min ± 18 min
						1207 ± 18 min	5 hr, 7 min ± 18 min
						1607 ± 18 min	9 hr, 7 min ± 18 min
						2007 ± 18 min	13 hr, 7 min ± 18 min
	24,4	0.000***	25.8%	83 ± 0.7	5 (24 hr)	0322	20 hr, 22 min
					2 (4 hr)	0005	17 hr, 5 min
						0405	24 hr, 5 min
						0805	4 hr, 5 min
						1205	8 hr, 5 min
						1605	12 hr, 5 min
						2005	16 hr, 5 min

NS = nonsignificant + = $p \leq 0.10$ (trend) * = $p \leq 0.05$ ** = $p \leq 0.01$ *** = $p \leq 0.001$

A were not found in the analysis of the first 24 hours of data:

Subject	Period not found to be significant
1	6 hr
2	6 hr (but found a 4 hr period)
4	6 hr, 12 hr

When comparing acrophase between Segment A and the first 24 hours of data, two acrophase were found not to overlap (Subjects 1 and 4)(Table 19). Thus, Subjects 1, 2, and 4 had differences between analyses and Subjects 3, 4, and 6 did not.

For Subjects 1, 2, and 4, Segment A had a total of 18.25-22.75 hours of data and this meant that in the first 24 hours of data analysis, 1.25-5.75 hours of data were added. These added hours included the data that was affected by respiratory therapy in all three subjects. For Subjects 3, 5, and 6 this was not the case. For Subject 3, respiratory therapy was never started so the addition of 5.75 hours to Segment A did not seem to affect findings. For Subjects 5 and 6, Segment A contained 24.75-25.5 hours of data. Respiratory therapy was not given during this time. Thus, differences seen in Subjects 1, 2, and 4 were probably due to the addition of data that were affected by the respiratory therapy.

Cosinor Analysis of Arrhythmia Data

Whole Data Set Analysis

Cosinor analysis of arrhythmia data (n=4) is summarized in Table 20. Significant 24-hour rhythms were found in PACs (n=1; R^2=5.8%), PVCs (n=2; R^2=3.2%-16.1%), and ventricular couplets (n=2; R^2=7.4%-8.1%). Significant 4-hour periods were found in PACs (n=1; R^2=2.8%), atrial tachycardia (n=1; R^2=3.6%), and PVCs (n=4; R^2=3.6%-9.7%). Significant rhythms with multiple periods (24 hr and 4 hr) were found in PACs (n=1;

Table 19

Comparison of Acrophases for Segment A and First 24 Hours of Heart Rate Data

Subject	Period (hr)	Acrophases[a] in Segment A	Acrophases[a] in first 24 hours	Comparison of acrophases
1	24	18 hr, 47 min ± 21 min	19 hr, 2 min ± 19 min	overlapping
	12	2 hr, 30 min ± 32 min	6 hr, 59 min ± 40 min	did not overlap by 3 hr, 17 min
	6	4 hr, 43 min ± 13 min	NS	6-hr rhythm gone in first 24 hr
	4	NS	NS	no change
2	24	17 hr, 46 min ± 26 min	17 hr, 59 min ± 28 min	overlapping
	12	3 hr, 52 min ± 38 min	3 hr, 48 min ± 41 min	overlapping
	6	4 hr, 58 min ± 20 min	NS	6-hr rhythm gone
	4	NS		4-hr rhythm appeared
3	24	22 hr, 59 min ± 41 min	22 hr, 29 min ± 30 min	overlapping
	12	NS	NS	no change
	6	NS	NS	no change
	4	NS	NS	no change
4	24	12 hr, 50 min ± 1 hr, 4 min	11 hr, 50 min ± 4 min	within 3 min of each other
	12	5 hr, 3 min ± 28 min	NS	12-hr rhythm gone
	6	1 hr, 53 min ± 11 min	NS	6-hr rhythm gone
	4	2 hr, 31 min ± 15 min	2 hr, 42 min ± 11 min	overlapping
5	24	15 hr, 27 min ± 37 min	15 hr, 24 min ± 39 min	overlapping
	12	5 hr, 47 min ± 13 min	5 hr, 47 min ± 13 min	same
	6	NS	NS	no change
	4	NS	NS	no change
6	24	20 hr, 39 min ± 43 min	20 hr, 24 min ± 45 min	overlapping
	12	NS	NS	no change
	6	NS	NS	no change
	4	1 hr, 13 min ± 16 min	1 hr, 7 min ± 18 min	overlapping

NS = nonsignificant

[a] Acrophases expressed in hours after customary midsleep

Table 20

Cosinor Analysis of Arrhythmias (N=4)

Subject	Variable	Period (hr)	Probability	R^2	Mesor ± SE (episodes in 15 min)	Half-amplitude (mesor to peak) (episodes in 15 min)	Acrophase ± SE (clock hr)	Acrophase (hr after customary midsleep)
1	PACs	24	0.004**	5.8%	43.± 3.7	17 ± 5.2	1714 ± 1hr, 10 min	15 hr, 14 min ± 1 hr, 10 min
	PACs	4	0.075+	2.8%	43 ± 3.8	12 ± 5.3	0146 ± 17 min	23 hr, 46 min ± 17 min
							0546 ± 17 min	3 hr, 46 min ± 17 min
							0946 ± 17 min	7 hr, 46 min ± 17 min
							1346 ± 17 min	11 hr, 46 min ± 17 min
							1746 ± 17 min	15 hr, 46 min ± 17 min
							2146 ± 17 min	19 hr, 46 min ± 17 min
	PACs	24,4	0.002**	8.7%	43 ± 3.7	17	1714	15 hr, 14 min
						12	0146	23 hr, 46 min
							0546	03 hr, 46 min
							0946	07 hr, 46 min
							1346	11 hr, 46 min
							1746	15 hr, 46 min
							2146	19 hr, 46 min
	AT	24	NS*					
	AT	4	0.034	3.6%	0.8 ± 0.1	0.5 ± 0.2	0102 ± 14 min	23 hr, 2 min ± 14 min
							0502 ± 14 min	3 hr, 2 min ± 14 min
							0902 ± 14 min	7 hr, 2 min ± 14 min
							1302 ± 14 min	11 hr, 2 min ± 14 min
							1702 ± 14 min	15 hr, 2 min ± 14 min
							2102 ± 14 min	19 hr, 2 min ± 14 min
	PVCs	24	NS***					
		4	0.000	9.7%	6 ± 0.7	4 ± 1.0	0059 ± 8.5 min	22 hr, 59 min ± 8.5 min
							0459 ± 8.5 min	2 hr, 59 min ± 8.5 min
							0859 ± 8.5 min	6 hr, 59 min ± 8.5 min
							1259 ± 8.5 min	10 hr, 59 min ± 8.5 min
							1659 ± 8.5 min	14 hr, 59 min ± 8.5 min
							2059 ± 8.5 min	18 hr, 59 min ± 8.5 min

table continues

Table 20 (continued)

Subject	Variable	Period (hr)	Probability	R^2	Mesor ± SE (episodes in 15 min)	Half-amplitude (mesor to peak) (episodes in 15 min)	Acrophase ± SE (clock hr)	Acrophase (hr after customary midsleep)
1	VCoup	24	0.001***	7.4%	0.1 ± 0.02	0.1 ± 0.03	0100 ± 59 min	23 hr ± 59 min
		4	NS					
	VT	24	NS					
		4	NS					
2	PACs	24	NS					
	PACs	4	NS					
	PVCs	24	NS*					
	PVCs	4	0.036*	3.6%	0.3 ± 0.1	0.2 ± 0.1	0359 ± 15 min	59 min ± 15 min
							0759 ± 15 min	4 hr, 59 min ± 15 min
							1159 ± 15 min	8 hr, 59 min ± 15 min
							1559 ± 15 min	12 hr, 59 min ± 15 min
							1959 ± 15 min	16 hr, 59 min ± 15 min
							2359 ± 15 min	20 hr, 59 min ± 15 min
3	PACs	24	NS					
	PACs	4	NS					
	PVCs	24	0.062+	3.2%	0.1 ± 0.03	0.1 ± 0.04	1309 ± 1 hr, 42 min	9 hr, 39 min ± 1 hr, 42 min
	PVCs	4	0.028*	4.1%	0.1 ± 0.03	0.1 ± 0.04	0306 ± 14 min	23 hr, 36 min ± 14 min
							0706 ± 14 min	3 hr, 36 min ± 14 min
							1106 ± 14 min	7 hr, 36 min ± 14 min
							1506 ± 14 min	11 hr, 36 min ± 14 min
							1906 ± 14 min	15 hr, 36 min ± 14 min
							2306 ± 14 min	19 hr, 36 min ± 14 min

table continues

Table 20 (continued)

Subject	Variable	Period (hr)	Probability	R^2	Mesor ± SE (episodes in 15 min)	Half-amplitude (mesor to peak) (episodes in 15 min).	Acrophase ± SE (clock hr)	Acrophase (hr after customary midsleep)
	PVCs	24,4	0.011*	7.3%	0.1 ± 0.03	0.1 (24 hr) 0.1 (4 hr)	1312 0306 0706 1106 1506 1906 2306	9 hr, 42 min 23 hr, 36 min 3 hr, 36 min 7 hr, 36 min 11 hr, 36 min 15 hr, 36 min 19 hr, 36 min
6	PVCs	24	0.000***	16.1%	23 ± 1.0	8 ± 1.4	0913 ± 42 min	2 hr, 13 min ± 42 min
	PVCs	4	0.001***	5.8%	23 ± 1.0	5 ± 1.4	0052 ± 12 min 0452 ± 12 min 0852 ± 12 min 1252 ± 12 min 1652 ± 12 min 2052 ± 12 min	17 hr, 52 min ± 12 min 21 hr, 52 min ± 12 min 1 hr, 52 min ± 12 min 5 hr, 52 min ± 12 min 9 hr, 52 min ± 12 min 13 hr, 52 min ± 12 min
	PVCs	24,4	0.000***	21.5%	23 ± 0.9	8 (24 hr) 5 (4 hr)	0915 0051 0451 0851 1251 1651 2051	2 hr, 15 min 17 hr, 51 min 21 hr, 51 min 1 hr, 51 min 5 hr, 51 min 9 hr, 51 min 13 hr, 51 min
	VCoup	24	0.001***	8.1%	0.5 ± 0.1	0.4 ± 0.1	0658 ± 58 min	23 hr, 58 min ± 58 min
		4	NS					
	VT	24	NS					
		4	NS					

NS, nonsignificant; PACs, premature atrial contractions; AT, atrial tachycardia; PVCs, premature ventricular contractions; V Coup, ventricular couplets; VT, ventricular tachycardia

+ = $p \leq 0.10$ (trend) * = $p \leq 0.05$ ** = $p \leq 0.01$ *** = $p \leq 0.001$

$\underline{R}^2$=8.7%) and PVCs ($\underline{n}$=2; $\underline{R}^2$=7.3%-21.5%). Acrophases for the significant rhythms in the arrhythmia data are summarized in Table 21. Acrophases for arrhythmias varied among individuals.

Within two subjects, some arrhythmias had overlapping acrophases. For Subject 1, the acrophase for the 24-hour rhythm in PACs overlapped with one of the acrophases for the 4-hour rhythms in PACs and atrial tachycardia. The acrophase of the 24-hour rhythm in ventricular couplets overlapped with one of the acrophases for the 4-hour rhythms in PACs, atrial tachycardia, and PVCs. For Subject 6, the acrophases of the 24-hour rhythm in PVCs overlapped with one of the acrophases of the 4-hour rhythm in PVCs, this overlapping of acrophases did not occur for Subject 3.

Acrophases for the 24-hour rhythms in ventricular couplets for Subjects 1 and 6 overlapped but did not for PVCs in Subjects 3 and 6. Acrophases for the 4-hour rhythm in PVCs (Subjects 1, 2, 3, and 4) did not overlap, but acrophases for Subjects 1 and 3 were quite similar.

Subject 1 was the only subject to have more than one arrhythmia with a significant 4-hour period. The acrophases of PVCs and atrial tachycardia overlapped; the acrophase of PACs did not overlap with the acrophases of PVCs and atrial tachycardia, but these acrophases were very similar. Figures 34-36 illustrate arrhythmia graphs with fitted cosine curves for each subject ($\underline{n}$=4).

Divided Data Set Analysis

Arrhythmia data were divided into two segments using the criteria listed previously in Table 16. Cosinor analysis was repeated on divided data. Table 22 summarizes analysis on Segments A and B for all

Table 21

Acrophases and Standard Error for Significant Periods in Arrhythmias Data (N=4)

Subject	Variable	Period (hr)	Acrophase ± SE (hr after customary midsleep)	Acrophase ± SE (decimal hr after customary midsleep)
1	PACs	24	15 hr, 14 min ± 1 hr, 10 min	15.23 ± 1.17(14.06-16.40)
	PACs	4	23 hr, 46 min ± 17 min	23.77 ± 0.28(23.49-24.05)
			3 hr, 46 min ± 17 min	3.77 ± 0.28(3.49-4.05)
			7 hr, 46 min ± 17 min	7.77 ± 0.28(7.49-8.05)
			11 hr, 46 min ± 17 min	11.77 ± 0.28(11.49-12.05)
			15 hr, 46 min ± 17 min	15.77 ± 0.28(15.49-16.05)
			19 hr, 46 min ± 17 min	19.77 ± 0.28(19.49-20.05)
	AT	4	23 hr, 2 min ± 14 min	23.03 ± 0.23(22.80-23.26)
			3 hr, 2 min ± 14 min	3.03 ± 0.23(3.80-3.26)
			7 hr, 2 min ± 14 min	7.03 ± 0.23(7.80-7.26)
			11 hr, 2 min ± 14 min	11.03 ± 0.23(11.80-11.26)
			15 hr, 2 min ± 14 min	15.03 ± 0.23(15.80-15.26)
			19 hr, 2 min ± 14 min	19.03 ± 0.23(19.80-19.26)
	PVCs	4	22 hr, 59 min ± 8.5 min	22.98 ± 0.15(22.83-23.13)
			2 hr, 59 min ± 8.5 min	2.98 ± 0.15(2.83-3.13)
			6 hr, 59 min ± 8.5 min	6.98 ± 0.15(6.83-7.13)
			10 hr, 59 min ± 8.5 min	10.98 ± 0.15(10.83-11.13)
			14 hr, 59 min ± 8.5 min	14.98 ± 0.15(14.83-15.13)
			18 hr, 59 min ± 8.5 min	18.98 ± 0.15(18.83-19.13)
	V Coup	24	23 hr ± 59 min	23.00 ± 0.98(22.02-23.98)
2	PVCs	4	59 min ± 15 min	0.98 ± 0.25(0.73-1.23)
			4 hr, 59 min ± 15 min	4.98 ± 0.25(4.73-5.25)
			8 hr, 59 min ± 15 min	8.98 ± 0.25(8.73-9.25)
			12 hr, 59 min ± 15 min	12.98 ± 0.25(12.73-13.25)
			16 hr, 59 min ± 15 min	16.98 ± 0.25(16.73-17.25)
			20 hr, 59 min ± 15 min	20.98 ± 0.25(20.73-21.25)

table continues

Table 21 (continued)

Subject	Variable	Period (hr)	Acrophase ± SE (hr after customary midsleep)	Acrophase ± SE (decimal hr after customary midsleep)
3	PVCs	24	9 hr, 39 min ± 1 hr, 42 min	9.65 ± 1.70(7.95-11.35)
	PVCs	4	23 hr, 36 min ± 14 min	23.60 ± 0.23(23.37-23.83)
			3 hr, 36 min ± 14 min	3.60 ± 0.23(3.37-3.83)
			7 hr, 36 min ± 14 min	7.60 ± 0.23(7.37-7.83)
			11 hr, 36 min ± 14 min	11.60 ± 0.23(11.37-11.83)
			15 hr, 36 min ± 14 min	15.60 ± 0.23(15.37-15.83)
			19 hr, 36 min ± 14 min	19.60 ± 0.23(19.37-19.83)
6	PVCs	24	2 hr, 13 min ± 42 min	2.22 ± 0.70(1.52-2.92)
		4	17 hr, 52 min ± 12 min	17.87 ± 0.20(17.67-18.07)
			21 hr, 52 min ± 12 min	21.87 ± 0.20(21.67-22.07)
			1 hr, 52 min ± 12 min	1.87 ± 0.20(1.67-2.07)
			5 hr, 52 min ± 12 min	5.87 ± 0.20(5.67-6.07)
			9 hr, 52 min ± 12 min	9.87 ± 0.20(9.67-10.07)
			13 hr, 52 min ± 12 min	13.87 ± 0.20(13.67-14.07)
	V Coup	24	23 hr, 58 min ± 58 min	23.97 ± 0.97(23.00-24.94)

SE, standard error; PACs, premature ventricular contractions; AT, atrial tachycardia;

PVCs, premature ventricular contractions; VCoup, ventricular couplets

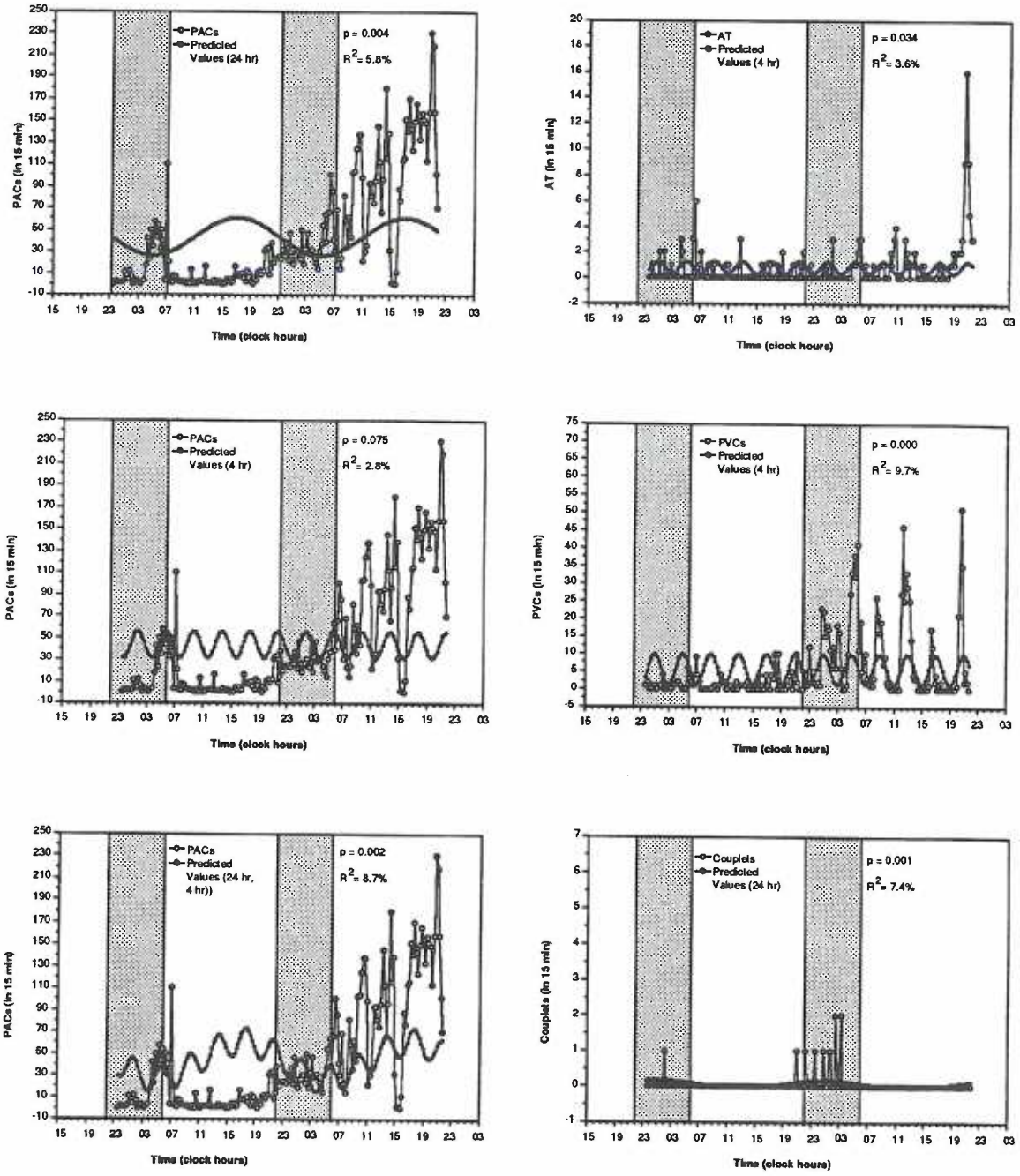


Figure 34. Graphs of arrhythmia data with fitted cosine curves for significant rhythms (PACs - 24 hr; 4 hr; and 24 hr and 4 hr. Atrial tachycardia - 4 hr. PVCs - 24 hr. Ventricular couplets-24 hr.) (Subject 1). Customary sleep time is shaded; this was not the sleep time during the study.

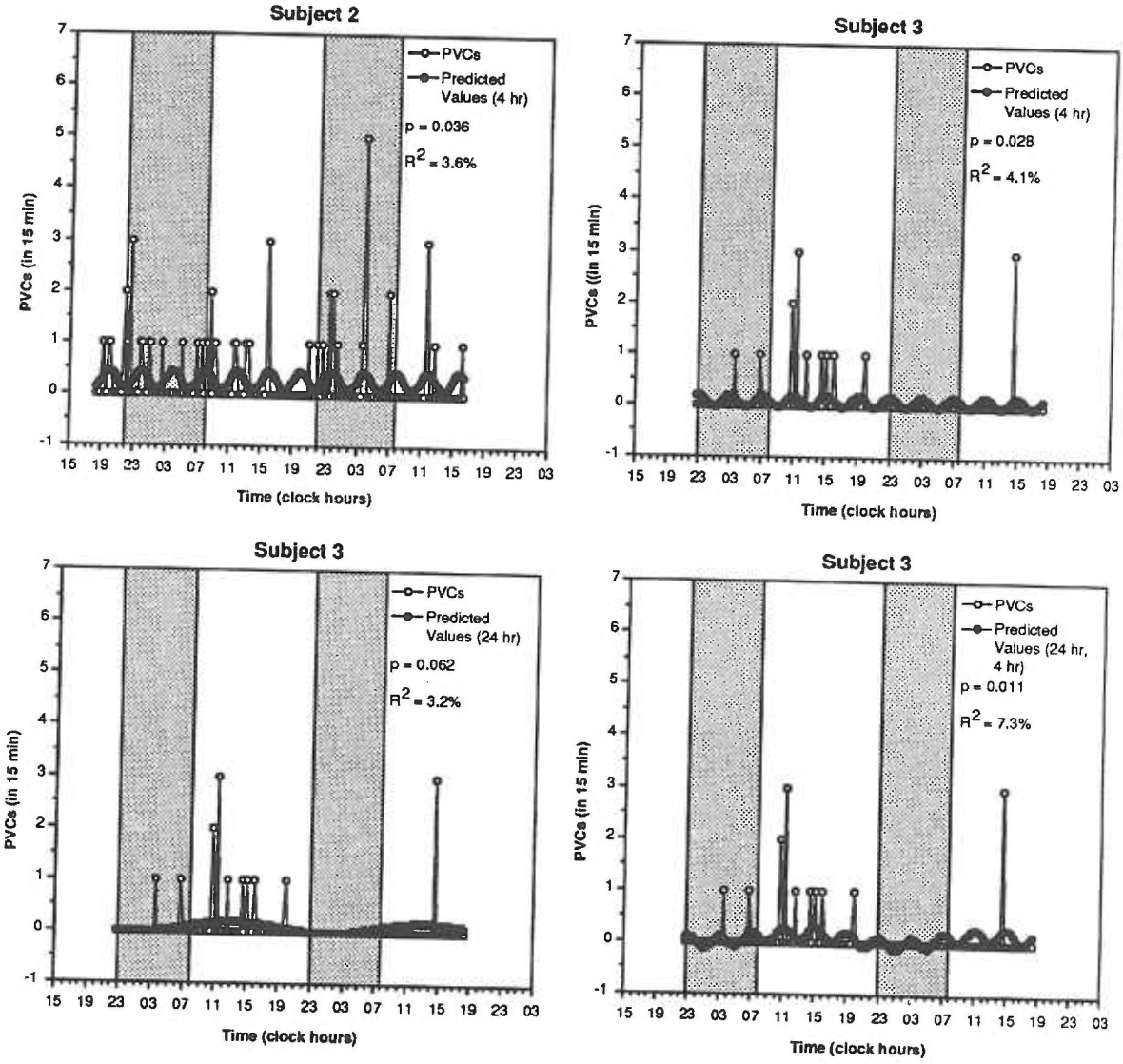


Figure 35. Graphs of arrhythmia data with fitted cosine curves for significant rhythms (Subject 2 - PVCs - 24 hr.) (Subject 3 - PVCs - 24 hr; 4 hr; 24 hr and 4 hr). Customary sleep time was shaded; this is not the sleep time during the study.

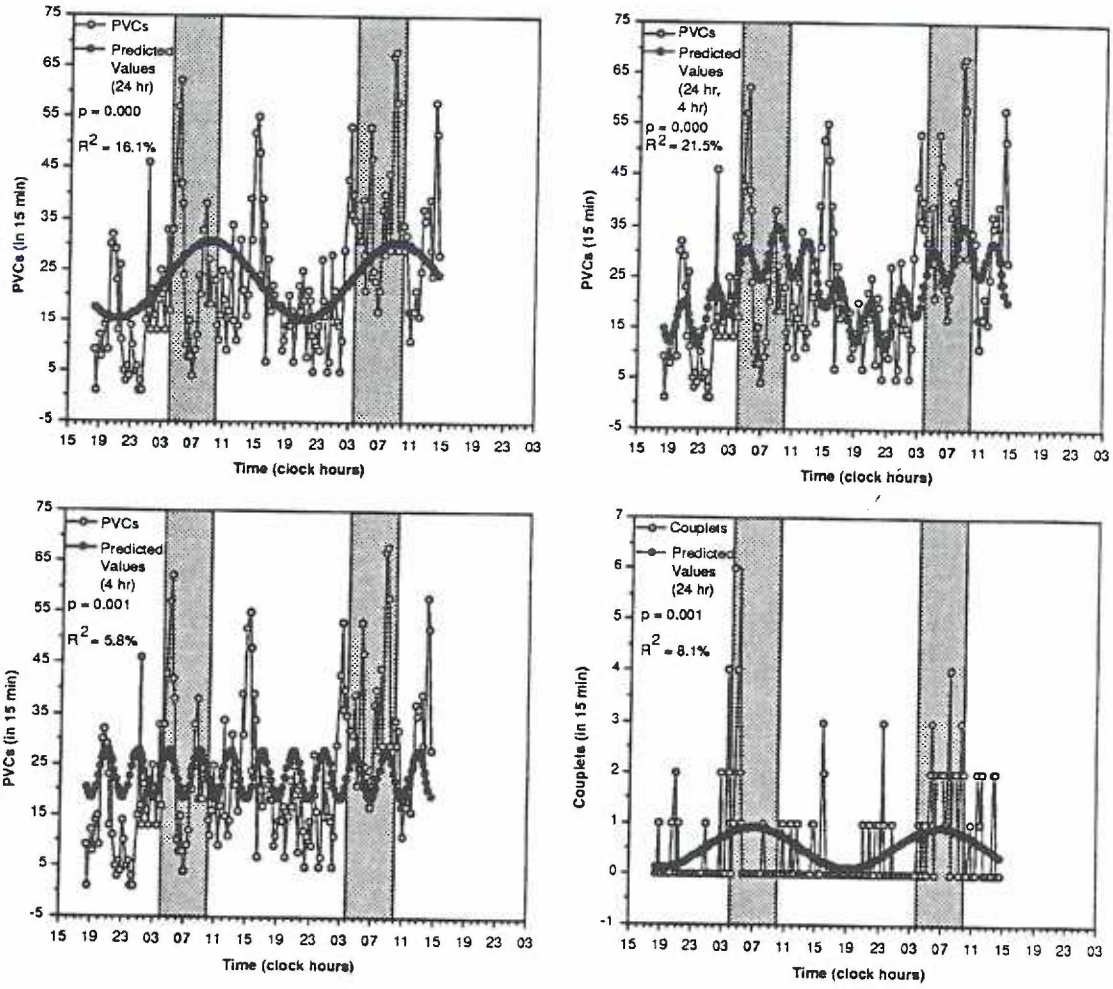


Figure 36. Graphs of arrhythmia data with fitted cosine curves for significant rhythms (PVCs - 24 hr; 4 hr; 24 hr and 4 hr. Ventricular couplets 24 hr)(Subject 6). Customary sleep time was shaded; this is not the sleep time during the study.

Table 22

Cosinor Analysis on Arrhythmias Data Divided into Two Segments (A and B) (N=4)

Subject	Variable	Period (hr)	Probability	R^2	Mesor ± SE (episodes in 15 min)	Half-amplitude (mesor to peak) (episodes in 15 min)	Acrophase ± SE (clock hr)	Acrophase (hr after customary midsleep)
1A	PACs	24	0.001***	17.1%	9 ± 1.9	10 ± 2.6	0538 ± 1 hr, 34 min	3 hr, 38 min ± 1 hr, 4 min
1B	PACs	24	0.000***	25.0%	69 ± 4.7	40 ± 6.6	1552 ± 37 min	13 hr, 52 min ± 37 min
1A	PACs	4	NS					
1B	PACs	4	0.089+	4.7%	69 ± 5.3	17 ± 7.5	0151 ± 17 min	23 hr, 51 min ± 17 min
							0551 ± 17 min	3 hr, 51 min ± 17 min
							0951 ± 17 min	7 hr, 51 min ± 17 min
							1351 ± 17 min	11 hr, 51 min ± 17 min
							1751 ± 17 min	15 hr, 51 min ± 17 min
							2151 ± 17 min	19 hr, 51 min ± 17 min
1B	PACs	24,4	0.000***	29.9%	69 ± 4.6	40(24 hr)	1550	13 hr, 50 min
						17(4 hr)	0152	23 hr, 52 min
							0552	3 hr, 52 min
							0952	7 hr, 52 min
							1352	11 hr, 52 min
							1752	15 hr, 52 min
							2152	19 hr, 52 min
1A	AT	24	NS					
1B	AT	24	NS					
1A	AT	4	NS					
1B	AT	4	0.029*	6.9%	1 ± 0.2	0.8 ± 0.3	0058 ± 14 min	22 hr, 58 min ± 14 min
							0458 ± 14 min	2 hr, 58 min ± 14 min
							0858 ± 14 min	6 hr, 58 min ± 14 min
							1258 ± 14 min	10 hr, 58 min ± 14 min
							1658 ± 14 min	14 hr, 58 min ± 14 min
							2058 ± 14 min	18 hr, 58 min ± 14 min

table continues

Table 22 (continued)

Subject	Variable	Period (hr)	Probability	R^2	Mesor ± SE (episodes in 15 min)	Half-amplitude (mesor to peak) (episodes in 15 min)	Acrophase ± SE (clock hr)	Acrophase (hr after customary midsleep)
1A	PVCs	24	NS					
1B	PVCs	24	0.011*	8.6%	9 ± 1.1	5 ± 1.6	0630 ± 1 hr, 16 min	4 hr, 30 min ± 1 hr, 16 min
1A	PVCs	4	0.019*	9.5%	1 ± 0.2	1 ± 0.3	0221 ± 13 min	21 min ± 13 min
							0621 ± 13 min	4 hr, 21 min ± 13 min
							1021 ± 13 min	8 hr, 21 min ± 13 min
							1421 ± 13 min	12 hr, 21 min ± 13 min
							1821 ± 13 min	16 hr, 21 min ± 13 min
							2221 ± 13 min	20 hr, 21 min ± 13 min
1B	PVCs	4	0.000***	21.1%	9 ± 1.0	8 ± 1.5	0056 ± 7 min	22 hr, 56 min ± 7 min
							0456 ± 7 min	2 hr, 56 min ± 7 min
							0856 ± 7 min	6 hr, 56 min ± 7 min
							1256 ± 7 min	10 hr, 56 min ± 7 min
							1656 ± 7 min	14 hr, 56 min ± 7 min
							2056 ± 7 min	18 hr, 56 min ± 7 min
1B	PVCs	24,4	0.000***	31.8%	9 ± 1.0	5 (24 hr)	0646	4 hr, 46 min
						8 (4 hr)	0056	22 hr, 56 min
							0456	2 hr, 56 min
							0856	6 hr, 56 min
							1251	10 hr, 56 min
							1656	14 hr, 56 min
							2056	18 hr, 56 min
1A	VCoup	24	NS					
1B	VCoup	24	0.003**	10.7%	0.1 ± 0.03	0.2 ± 0.05	0135 ± 1 hr, 3 min	23 hr, 36 min ± 1 hr, 3 min

table continues

Table 22 (continued)

Subject	Variable	Period (hr)	Probability	R^2	Mesor ± SE (episodes in 15 min)	Half-amplitude (mesor to peak) (episodes in 15 min)	Acrophase ± SE (clock hr)	Acrophase (hr after customary midsleep)
2A	PVCs	24	NS					
2B	PVCs	24	NS					
2A	PVCs	4	NS					
2B	PVCs	4	0.020*	6.9%	0.2 ± 0.1	0.3 ± 0.1	0356 ± 13 min	56 min ± 13 min
							0756 ± 13 min	4 hr, 56 min ± 13 min
							1156 ± 13 min	8 hr, 56 min ± 13 min
							1556 ± 13 min	12 hr, 56 min ± 13 min
							1956 ± 13 min	16 hr, 56 min ± 13 min
							2356 ± 13 min	20 hr, 56 min ± 13 min
3A	PVCs	24	NS					
3B	PVCs	24	NS					
3A	PVCs	4	0.059+	7.8%	0.1 ± 0.1	0.2 ± 0.1	0309 ± 16 min	23 hr, 39 min ± 16 min
							0709 ± 16 min	3 hr, 39 min ± 16 min
							1109 ± 16 min	7 hr, 39 min ± 16 min
							1509 ± 16 min	11 hr, 39 min ± 16 min
							1909 ± 16 min	15 hr, 39 min ± 16 min
							2309 ± 16 min	19 hr, 39 min ± 16 min
3B	PVCs	4	NS					
6A	PVCs	24	0.026***	7.3%	20 ± 1.3	5 ± 1.8	1014 ± 1 hr, 22 min	3 hr, 14 min ± 1 hr, 22 min
6B	PVCs	24	0.000	29.7%	26 ± 1.4	11 ± 2.2	0849 ± 46 min	1 hr, 49 min ± 46 min

table continues

Table 22 (continued)

Subject	Variable	Period (hr)	Probability	R^2	Mesor ± SE (episodes in 15 min)	Half-amplitude (mesor to peak) (episodes in 15 min)	Acrophase ± SE (clock hr)	Acrophase (hr after customary midsleep)
6A	PVCs	4	0.014*	8.5%	20 ± 1.3	5 ± 1.8	0045 ± 13 min	17 hr, 45 min ± 13 min
							0445 ± 13 min	21 hr, 45 min ± 13 min
							0845 ± 13 min	1 hr, 45 min ± 13 min
							1245 ± 13 min	5 hr, 45 min ± 13 min
							1645 ± 13 min	9 hr, 45 min ± 13 min
							2045 ± 13 min	13 hr, 45 min ± 13 min
6B	PVCs	4	NS					
6A	PVCs	24,4	0.003**	15.4%	20 ± 1.2	5 (24 hr)	1024	3 hr, 24 min
						5 (4 hr)	0046	17 hr, 46 min
							0446	21 hr, 46 min
							0846	1 hr, 46 min
							1246	5 hr, 46 min
							1646	9 hr, 46 min
							2046	13 hr, 46 min
6A	VCoup	24	NS					
6B	VCoup	24	0.000***	18.3%	0.6 ± 0.1	0.6 ± 0.2	0819 ± 1 hr, 1 min	1 hr, 19 min ± 1 hr, 1 min
6A	VCoup	4	0.068+	5.4%	0.4 ± 0.1	0.3 ± 0.1	0024 ± 17 min	17 hr, 24 min ± 17 min
							0424 ± 17 min	21 hr, 24 min ± 17 min
							0824 ± 17 min	1 hr, 24 min ± 17 min
							1224 ± 17 min	5 hr, 24 min ± 17 min
							1624 ± 17 min	9 hr, 24 min ± 17 min
							2024 ± 17 min	13 hr, 24 min ± 17 min
6B	VCoup	4	NS					

NS, nonsignificant; PACs, premature atrial contractions; AT, atrial tachycardia; PVCs, premature ventricular contractions; VCoup, ventricular couplets.

+ = $p \leq 0.10$ (trend) * = $p \leq 0.05$ ** = $p \leq 0.01$ *** = $p \leq 0.001$

subjects. Figures 37-39 illustrate arrhythmia graphs with fitted cosine curves for Segments A and B. Findings between whole data set analysis and this analysis were similar for the number of 24-hour rhythms found except for PVCs in Subjects 1 and 3. In Subject 1, a significant 24-hour rhythm was found in Segment B only; in Subject 3 a trend toward significance was found in the whole data set but not in either segment.

Findings of the number of 4-hour rhythms in arrhythmias were inconsistent between whole data set analysis and divided data analysis:

Subject	Arrhythmia	Whole Data	Segment A	Segment B
1	PACs	T	NS	S
1	AT	S	NS	S
1	PVCs	S	S	S
2	PVCs	S	NS	S
3	PVCs	S	T	NS
6	PVCs	S	S	NS
6	VCoups	NS	T	NS

Note. T = trend S = significant NS = nonsignificant

Explained variance (R^2) increased considerably (4.7%-31.8%) when segments were analyzed separately and was different between Segments A and B. Explained variance (R^2) for the significant 24-hour periods is listed for Segments A and B for each subject:

Subject	Arrhythmia	Segment A	Segment B
1	PACs	17.1%	25.0%
	PVCs		8.6%
	VCoup		10.7%
6	PVCs	7.3%	29.7%
	VCoup		18.3%

Mesors, amplitudes, and acrophases were also different between Segments A and B. Acrophases (in hours after customary midsleep) for 24-hour rhythms in arrhythmias are listed:

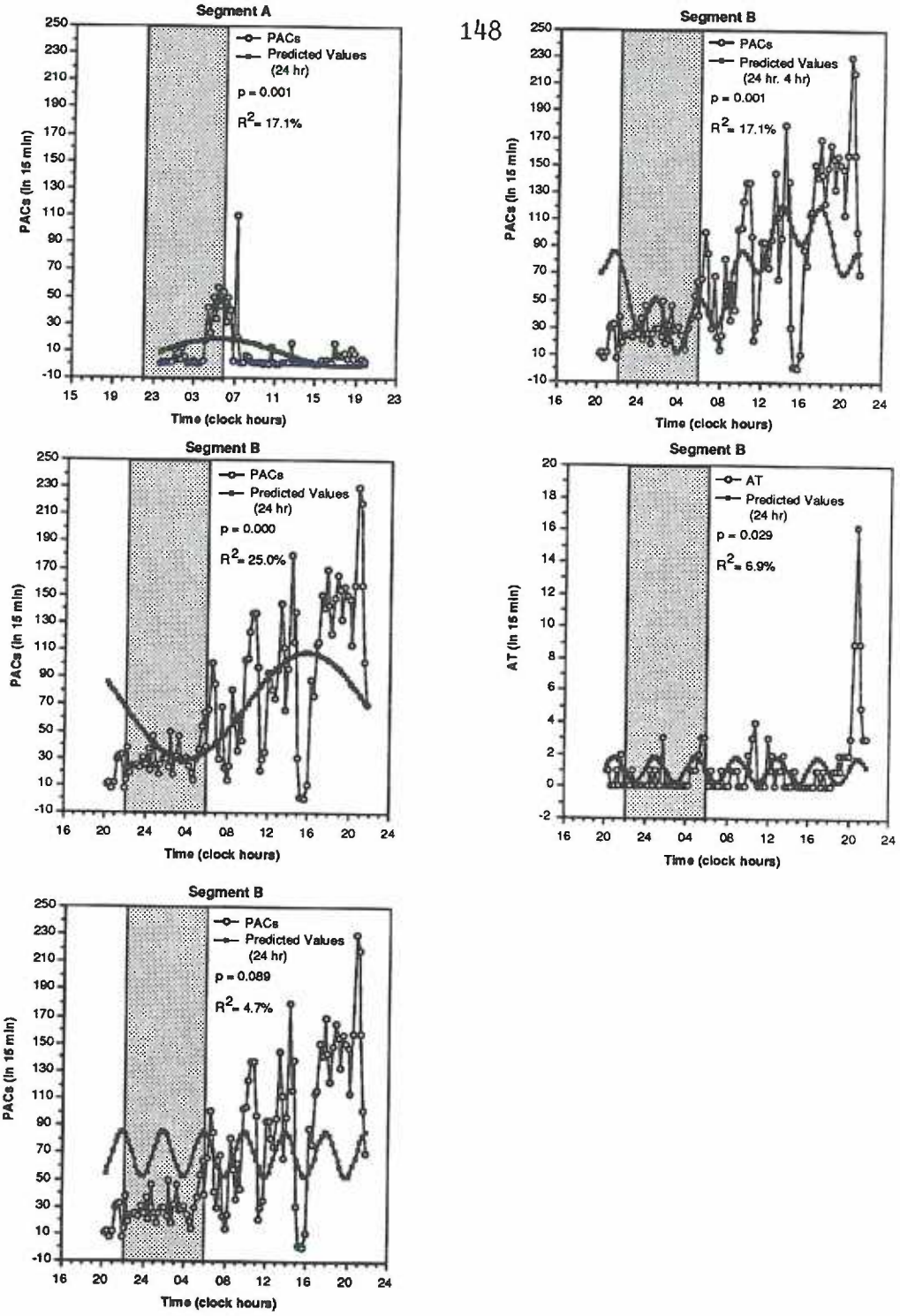


Figure 37. Graphs of atrial arrhythmia data with fitted cosine curves for significant rhythms in Segment A (PACs - 24 hr) and in Segment B (PACs - 24 hr; 4 hr; 24 hr and 4 hr. Atrial tachycardia - 4 hr) (Subject 1). Customary sleep time is shaded; this was not the sleep time during the study.

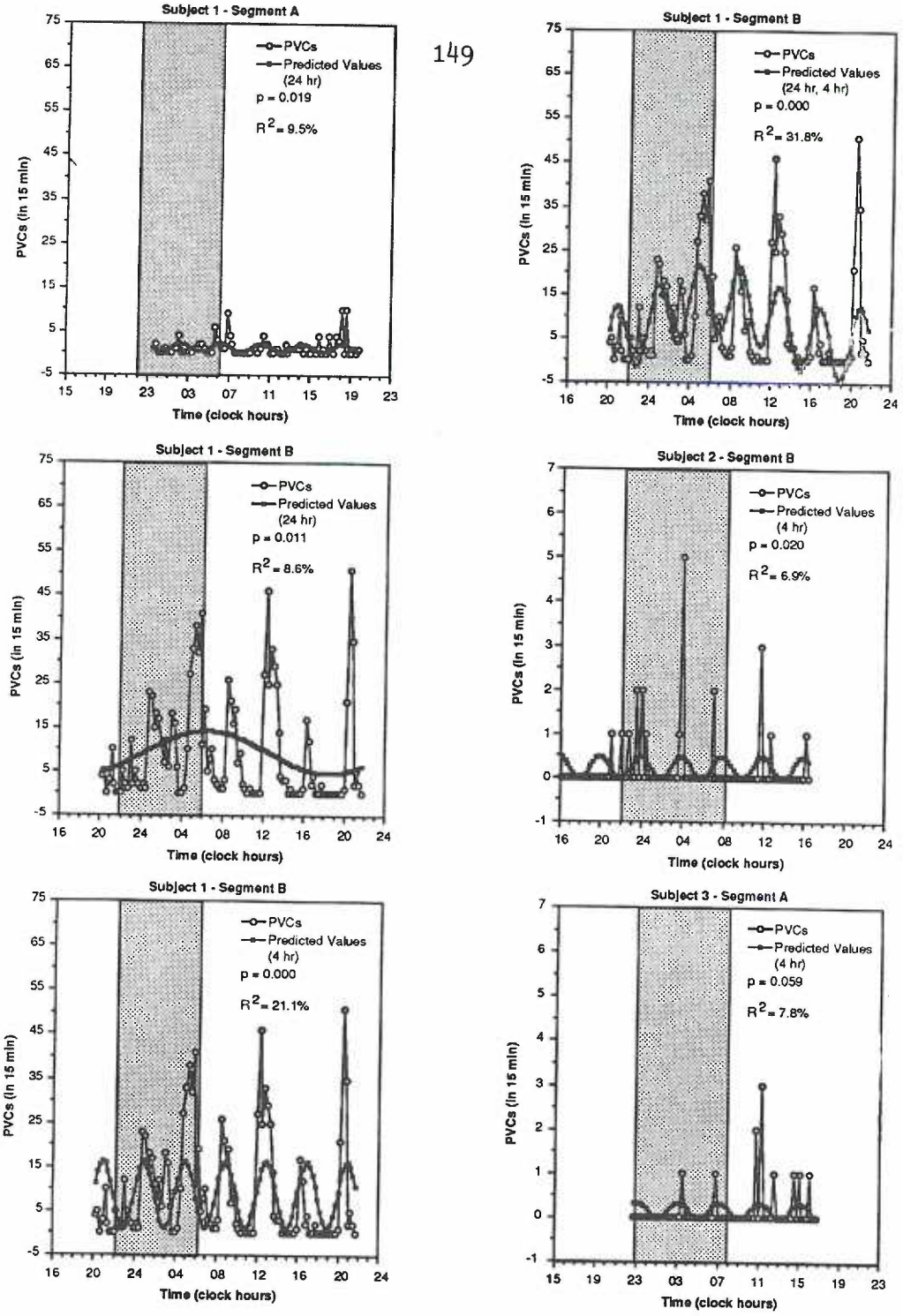


Figure 38. Graphs of ventricular arrhythmia data with fitted cosine curves for significant rhythms. (Subject 1 - PVCs Segment A, 4 hr; PVCs Segment B, 24 hr, 4 hr, and 24 hr and 4 hr. Subject 2 - PVCs Segment B, 4 hr. Subject 3 - PVCs Segment A, 4 hr). Customary sleep time is shaded; this was not the sleep time during the study.

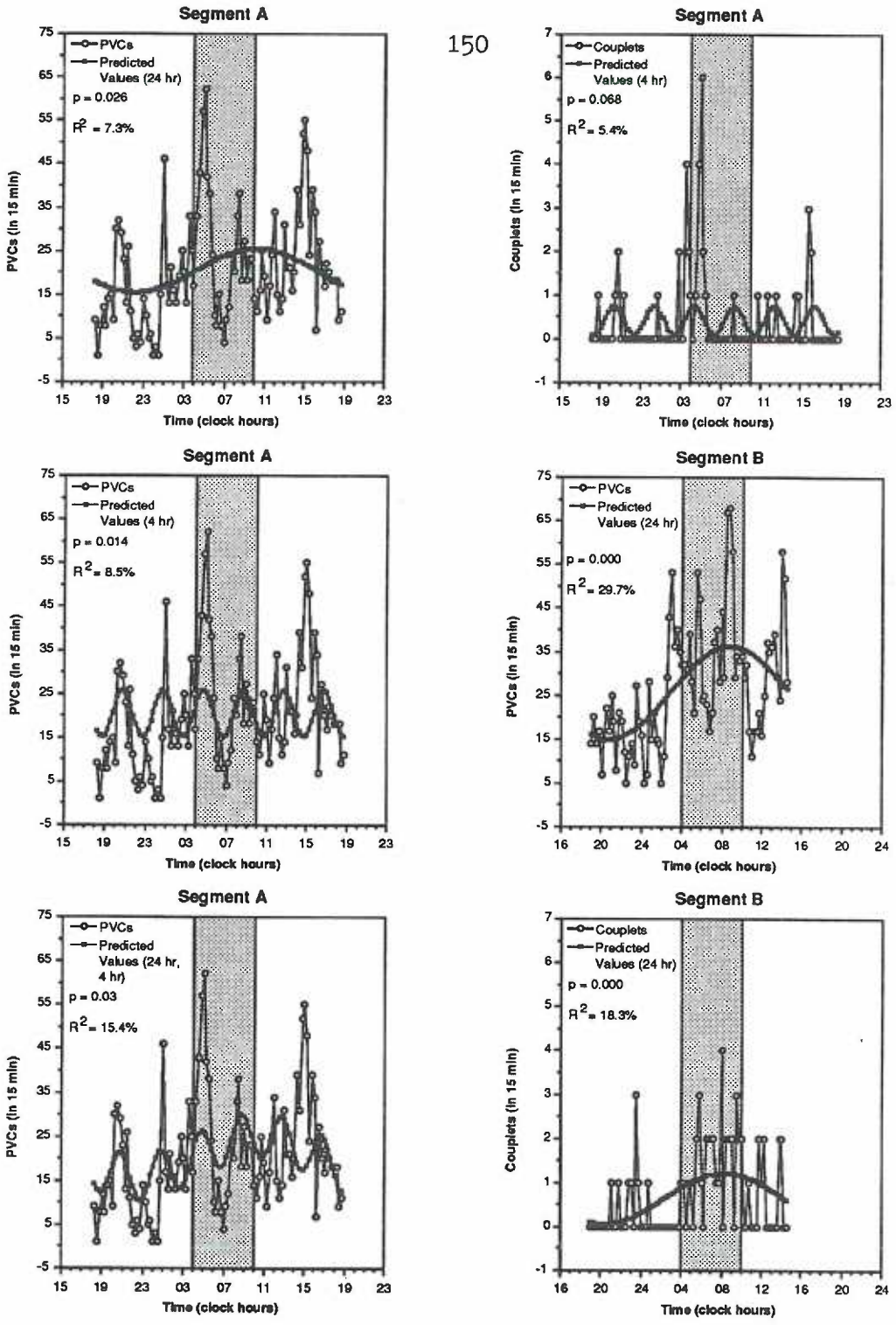


Figure 39. Graphs of ventricular arrhythmias with fitted cosine curves for significant rhythms in Segment A (PVCs - 24 hr; 4 hr; 24 hr and 4 hr. Ventricular couplets - 4 hr) and in Segment B (PVCs - 24 hr. Ventricular couplets - 24 hr) (Subject 6). Customary sleep time is shaded; this was not the sleep time during the study.

Subject	Arrhythmia	Segment A	Segment B
1	PACs	3 hr, 38 min ± 1 hr, 4 min	13 hr, 52 min ± 37 min
1	PVCs		4 hr, 30 min ± 1 hr, 16 min
1	VCoup		23 hr, 36 min ± 1 hr, 3 min
6	PVCs	3 hr, 14 min ± 1 hr, 22 min	1 hr, 49 min ± 46 min
6	VCoup		1 hr, 19 min ± 1 hr, 1 min

For Subject 6, PVCs and ventricular couplets had overlapping acrophases in Segment B of the data. For Subject 6, Rhythms of PVCs and ventricular couplets in Segment B and rhythms of PVCs and ventricular couplets in the whole data set had overlapping acrophases.

Acrophases for PVC rhythms between the whole data set and Segments A and B are summarized in Table 23. PVC acrophases overlapped in Subject 6's 24-hour rhythm in PVCs in whole data set and Segments A and B. Acrophases overlapped in Subject 1's 4-hour rhythm in PVCs in the whole data set and Segment B but not in Segment A. In no other case did the significant rhythms occur in the whole data set and in both segments. The acrophases of the 4-hour rhythms of PVCs overlapped in Subject 1 and 2 between whole data set and Segment B, and in Subjects 3 and 6 between whole data set and A. Subjects 1 and 2 both received respiratory therapy in Segment B.

In Subject 1 rhythms in PACs in Segment B and PACs in the whole data set had overlapping acrophases as did atrial tachycardia.

Temporal Pattern in Cardiac Output and Stroke Volume

Cardiac output was measured every 1-4 hours. Data were eliminated from the analysis using the criteria previously listed in Table 11. Total number of hours of cardiac output and stroke volume data that was used in the analysis ranged from 25-45.75 hours (Table 24).

Graphical Analysis of Cardiac Output and Stroke Volume

Cardiac output and stroke volume were graphed over time (Figure

Table 23

Comparison of Acrophases for PVC Rhythms Between the Whole Data Set and Segments A and B (N=4)

Subject	Period (hr)	Acrophase whole data set (hr after customary midsleep)	Acrophase Segment A (hr after customary midsleep)	Acrophase Segment B (hr after customary midsleep)	Comparison of acrophases
1	24	NS	NS	4 hr, 30 min ± 1 hr, 16 min	24-hr rhythm in B only.
	4	2 hr, 59 min ± 8.5 min	21 min ± 13 min	2 hr, 56 min ± 7 min	Overlap between whole data set and B.
2	24	NS	NS	NS	No change.
	4	59 min ± 15 min	NS	56 min ± 13 min	No 4-hr rhythm in A.
3	24	9 hr, 39 min ± 1 hr, 42 min	NS	NS	No 24-hr rhythm in A or B.
	4	3 hr, 36 min ± 14 min	3 hr, 39 min ± 16 min	NS	No 4-hr rhythm in B.
6	24	2 hr, 13 min ± 42 min	3 hr, 14 min ± 1 hr 22 min	1 hr, 49 min ± 46 min	Overlap.
	4	1 hr, 52 min ± 12 min	1 hr, 45 min ± 13 min	NS	No 4-hr rhythm in B.

NS = nonsignificant

Table 24

Total Number of Hours of Cardiac Output and Stroke Volume Data Used for Analysis

Subject	Data collection time	Total hr
1	Day 1, 24.00[a] through Day 3, 15.00	39.00
2	Day 1, 18.25 through Day 3, 16.00	45.75
3	Day 1, 23.00 through Day 2, 24.00	25.00
4	Day 1, 16.00 through Day 3, 04.00	36.00
5	Day 1, 18.00 through Day 2, 22.00	28.00
6	Day 1, 18.50 through Day 3, 15.00	44.50

[a] Time in decimal clock hours.

40) and were found to generally parallel each other. As with heart rate and rhythm, treatment and environmental variables were noted on the graphs. Variables thought to affect cardiac output and stroke volume were examined to determine their effects. Increases and decreases in cardiac output and stroke volume were examined to see if environmental or treatment variables were related to changes in values. The following seemed to be related to an increased cardiac output and stroke volume: suctioning, respiratory therapy, extubation, shivering, bed bath, position change, turning, sitting up in bed for a chest x-ray film, sitting at the bedside with feet dangling, turning, and sitting in the chair. Cardiac output and stroke volume appeared to decrease when the patient was sleeping undisturbed and when intravascular volume was low. Cardiac output and stroke volume were higher during the last segment of data collection in Subjects 2 and 3, while lower overall values were seen in Subjects 4 and 5.

Cardiac output and stroke volume were expected to decrease during the time of customary midsleep. Decreases could be seen in Subjects 1, 2, and 4, but not in the other three. Previous studies of normal individuals have shown increases in cardiac output 9.1-15.3 hours after midsleep and in stroke volume 7.2-11.4 hours after midsleep (Smolensky et al., 1976b). These increases were seen in Subjects 1, 2, 3, and 4 but not in Subjects 5 and 6.

Cardiac output (index) and stroke volume (index) had a wide range during data collection. Table 25 lists minimum and maximum values for each subject.

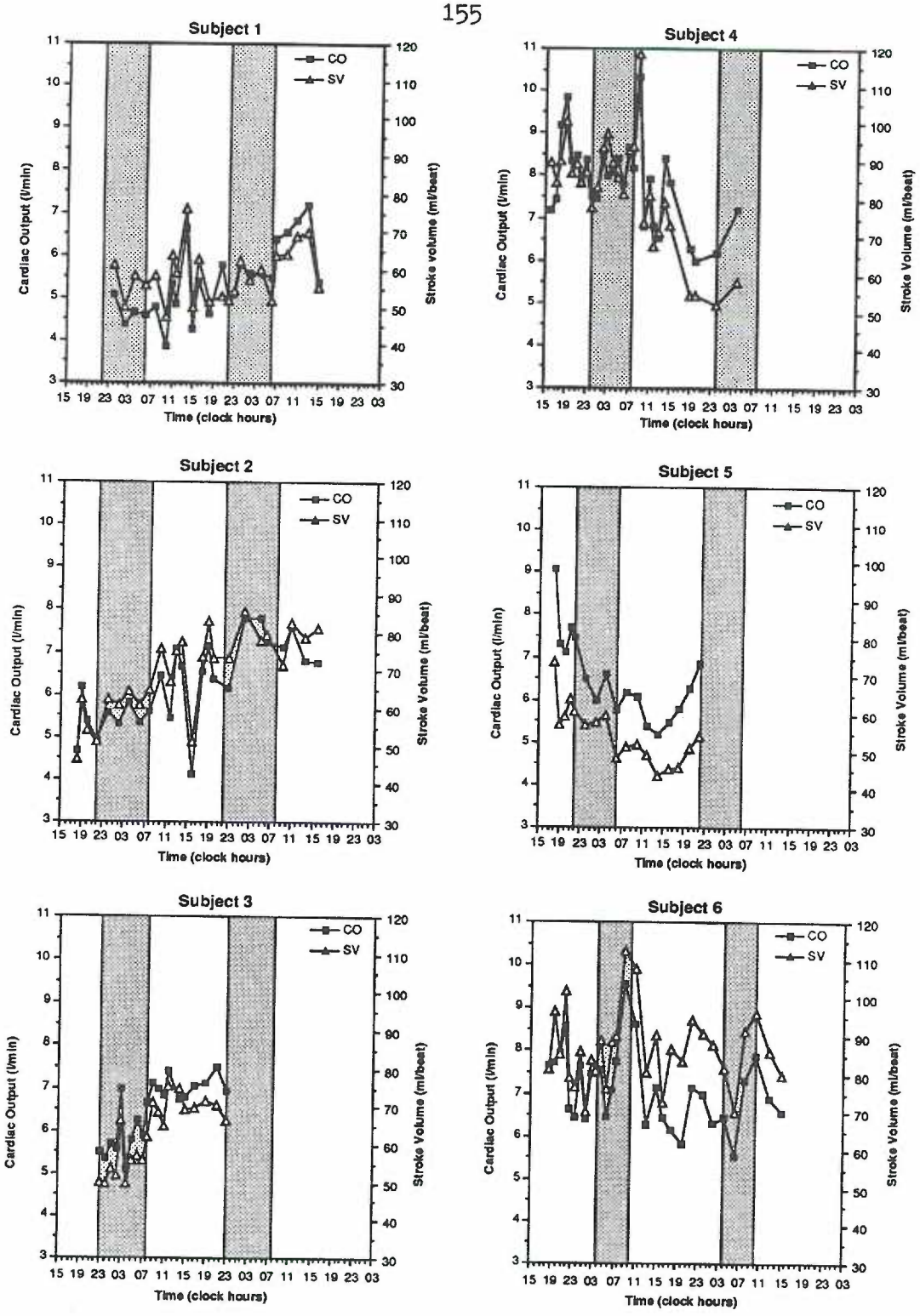


Figure 40. Graphs of cardiac output and stroke volume data over time. Customary sleep time is shaded; this was not the sleep time during the study.

Table 25

Cardiac Output, Cardiac Index, Stroke Volume, and Stroke Index: Minimum and Maximum Values During the Study

Subject	Body surface area	CO (l/min)		CI (l/min/m^2)		SV (ml/beat)		SI (ml/beat/m^2)	
		Min	Max	Min	Max	Min	Max	Min	Max
1	1.92	3.87	7.22	2.02	3.76	47.77	76.44	24.88	39.81
2	1.80	4.11	7.80	2.28	4.33	46.80	85.49	26.00	47.49
3	1.61	5.12	7.49	3.18	4.65	49.71	75.51	30.88	46.90
4	1.87	6.00	10.31	3.21	5.51	52.02	118.51	27.82	63.37
5	1.55	5.18	9.06	3.34	5.85	43.90	73.66	28.32	47.52
6	1.80	5.54	9.55	3.08	5.31	70.13	112.35	38.96	62.42

CO, cardiac output; CI, cardiac index; SV, stroke volume; SI, stroke index; min, minimum; max, maximum

Cosinor Analysis of Cardiac Output and Stroke Volume

Cosinor analysis of cardiac output is summarized in Table 26. A significant 24-hour rhythm was found in Subject 3 (p=0.006; R^2=45.6%) and Subject 5 (p=0.056; R^2=33.7%), with similar mesors and amplitudes, and nonoverlapping acrophases (Table 27). Subject 3 had an acrophase during the expected time interval for normals while Subject 5 did not. Because heart rate was found to have a significant 12-hour rhythm in Subjects 1 and 5, this period was evaluated in cardiac output data for these two subjects and found to be nonsignificant. No significant 4-hour rhythms of cardiac output were found in any of the subjects. Cardiac output graphs with fitted cosine curves are shown in Figure 41.

Cosinor analysis of stroke volume is summarized in Table 28. Subjects 3 and 5 who had 24-hour cardiac output rhythms also had significant 24-hour rhythms of moderate amplitude (Suject 3, p<0.001, R^2=63%; Subject 5, p=0.096, R^2=28.4%) in stroke volume. Mesor and amplitudes were higher for Subject 3 than for Subject 5. Acrophases did not overlap. Subject 3's acrophase occurred in the time interval expected for normals. No significant 4-hour rhythm were found in stroke volume. Stroke volume graphs with fitted cosine curves are illustrated in Figure 42.

Variables with Significant Periods for Each Subject

Table 29 summarizes all study variables in the whole data set and in the divided data set analysis with significant rhythms for each subject. Table 30 lists acrophases for all significant rhythms for all subjects for whole data set analysis and for divided data set analysis.

Table 26

Cosinor Analysis of Cardiac Output

Subject	Period (hr)	Probability	R^2	Mesor ± SE (1/min)	Half-amplitude ± SE (mesor to peak) (1/min)	Acrophase ± SE (clock hr)	Acrophase (hr after customary midsleep)
1	24	NS					
	12	NS					
	4	NS					
2	24	NS					
	4	NS					
3	24	0.006**	45.6%	6.57 ± 0.13	0.7 ± 0.2	1448 ± 1 hr	11 hr, 18 min ± 1 hr
	4	NS					
4	24	NS					
	4	NS					
5	24	0.056+	33.7%	6.30 ± 0.22	0.8 ± 0.3	2150 ± 1 hr, 35 min	19 hr, 50 min ± 1 hr, 35 min
	12	NS					
	4	NS					
6	24	NS					
	4	NS					

NS = nonsignificant + = $p \leq 0.10$ (trend) * = $p \leq 0.05$ ** = $p \leq 0.01$ *** = $p \leq 0.001$

Table 27

Acrophases and Standard Error for Significant Rhythms in Cardiac Output and Stroke Volume (N=2)

Subject	Variable	Period (hr)	Acrophase ± SE (hr after customary midsleep)	Acrophase ± SE (decimal hr after customary midsleep)
3	CO	24	11 hr, 18 min ± 1 hr	11.30 ± 1(10.30-12.30)
5	CO	24	19 hr, 50 min ± 1 hr, 35 min	19.83 ± 1.58(18.25-21.41)
3	SV	24	11 hr, 15 min ± 42 min	11.25 ± 0.70(10.55-11.95)
5	SV	24	21 hr, 23 min ± 1 hr, 35 min	21.38 ± 1.58(19.80-22.96)

SE, standard error; CO, cardiac output; SV, stroke volume

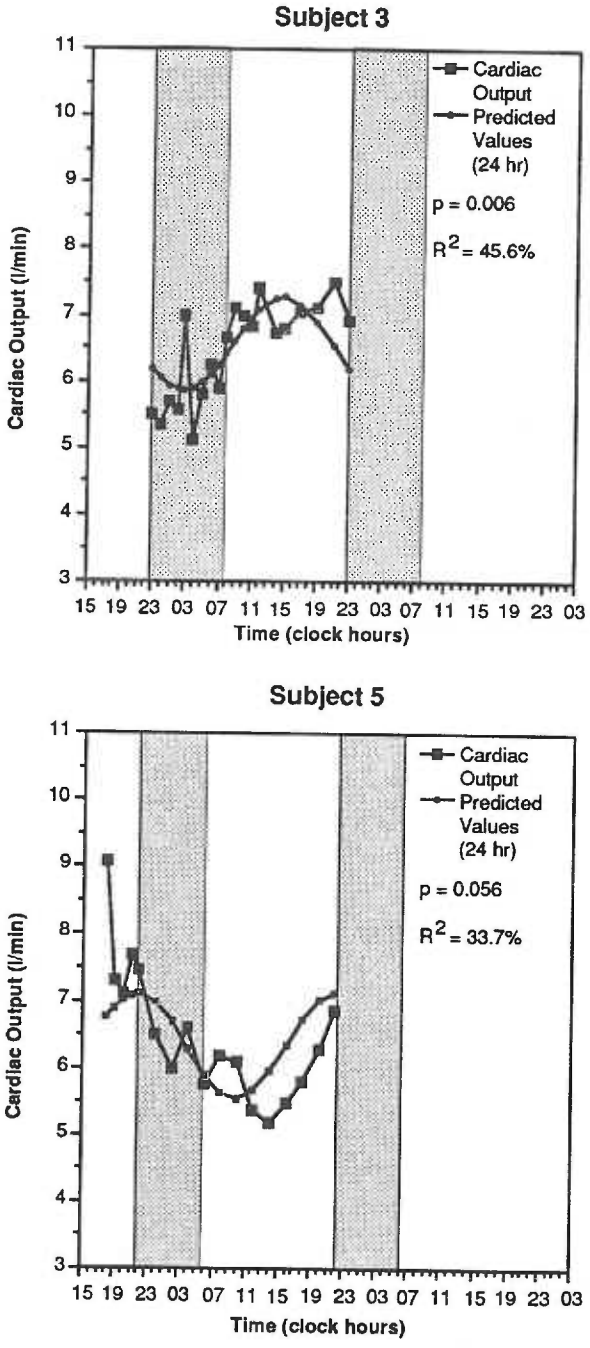


Figure 41. Graphs of cardiac output data with fitted cosine curves for significant 24 hour rhythms (Subjects 3 and 5). Customary sleep time is shaded; this was not the sleep time during the study.

Table 28

Cosinor Analysis of Stroke Volume

Subject	Period (hr)	Probability	R^2	Mesor ± SE (ml/beat)	Half-amplitude ± SE (mesor to peak) (ml/beat)	Acrophase ± SE (clock hr)	Acrophase (hr after customary midsleep)
1	24	NS					
	4	NS					
2	24	NS					
	4	NS					
3	24	0.000***	63.0%	64.30 ± 1.32	9.89 ± 1.80	1445 ± 42 mins	11 hr, 15 min ± 42 min
	4	NS					
4	24	NS					
	4	NS					
5	24	0.096+	28.4%	53.70 ± 1.78	5.9 ± 2.6	2323 ± 1 hr, 35 min	21 hr, 23 min ± 1 hr, 35 min
	4	NS					
6	24	NS					
	4	NS					

NS = nonsignificant + = $p \leq 0.10$ (trend) * = $p \leq 0.05$ ** = $p \leq 0.01$ *** = $p \leq 0.001$

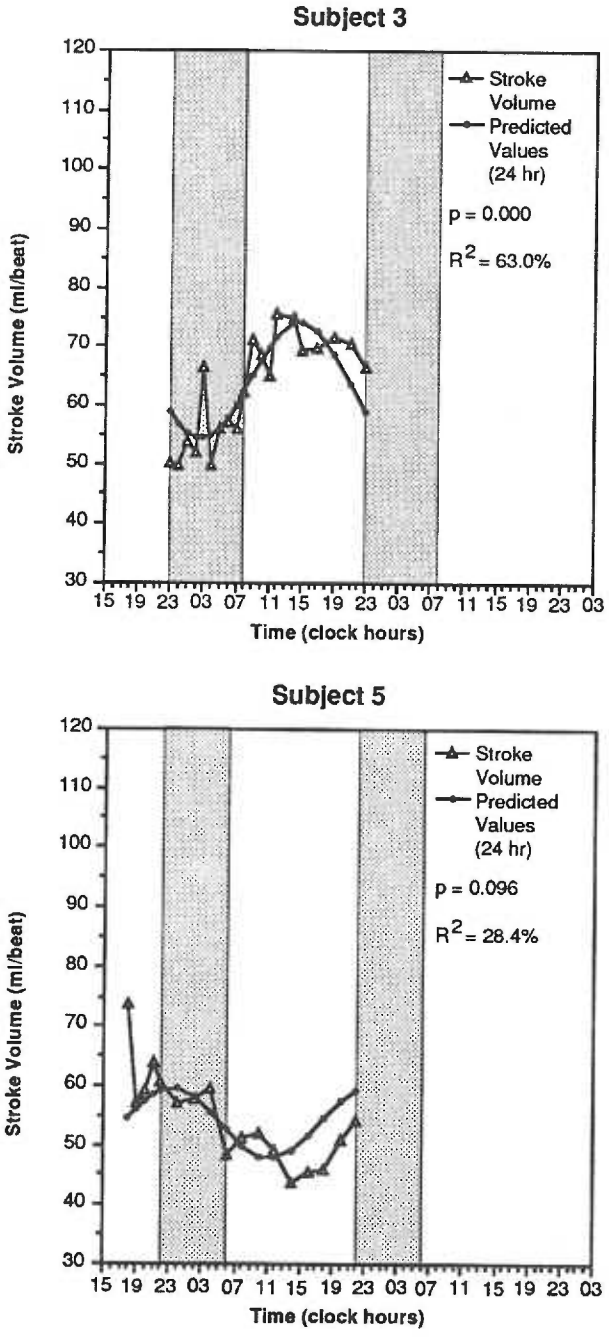


Figure 42. Graphs of stroke volume data with fitted cosine curves for significant 24 hour rhythms (Subjects 3 and 5). Customary sleep time is shaded; this was not the sleep time during the study.

Table 29

Summary of Significant Rhythms for Each Subject for All Study Variables in Whole Data Set and in Divided Data Set (A and B)

Variable	Period (hr)	Subject 1 WD	Subject 1 A	Subject 1 B	Subject 2 WD	Subject 2 A	Subject 2 B	Subject 3 WD	Subject 3 A	Subject 3 B	Subject 4 WD	Subject 4 A	Subject 4 B	Subject 5 WD	Subject 5 A	Subject 5 B	Subject 6 WD	Subject 6 A	Subject 6 B	Total number WD	Total number A	Total number B
HR (N=6)	24	*	***	+	***	***	***	NS	***	***	+	**	***	**	***	***	***	***	***	n=5	N=6	N=6
	12	+	**	**	NS	**	NS	NS	NS	NS	NS	***	*	***	***	NS	NS	NS	NS	n=2	n=4	n=2
	6	NS	***	NS	NS	*	*	NS	NS	*	NS	***	NS	NS	NS	***	NS	NS	+	n=0	n=3	n=4
	4	*	NS	***	***	NS	***	NS	NS	NS	NS	*	+	NS	NS	NS	NS	*	NS	n=2	n=2	n=3
PACs (n=3)	24	**	***	***	NS			NS				---			---			---		n=1	n=1	n=1
	4	+	NS	+	NS			NS				---			---			---		n=1	n=0	n=1
AT (n=1)	24	NS	NS	NS		---			---			---			---			---		n=0	n=0	n=0
	4	*	NS	*		---			---			---			---			---		n=1	n=0	n=1
PVCs (n=4)	24	NS	NS	*	NS	NS	NS	+	NS	NS		---			---		***	*	***	n=2	n=1	n=2
	4	***	NS	***	*	NS	*	*	+	NS		---			---		***	*	NS	n=4	n=2	n=2
VCoup (n=2)	24	***	NS	**		---			---			---			---		***	NS	***	n=2	n=0	n=2
	4	NS				---			---			---			---		NS	+	NS	n=0	n=1	n=0
VT (n=2)	24	NS				---			---			---			---		NS			n=0		
	4	NS				---			---			---			---		NS			n=0		
CO (N=6	24	NS			NS			**			NS			+			NS			n=2		
	12	---			---			NS			---			NS			---			n=0		
	4	NS			NS			NS			NS			NS			NS			n=0		
SV (N=6)	24	NS			NS			***			NS			+			NS			n=2		
	4	NS			NS			NS			NS			NS			NS			n=0		

HR, heart rate; PACs, premature atrial contractions; AT, atrial tachycardia; PVCs, premature ventricular contractions; VCoup, premature ventricular contractions; VT, ventricular tachycardia; CO, cardiac output; SV, stroke volume; WD, whole data set; A, Segment A; and B, Segment B; NS, nonsignificant; $p \leq 0.10$ (trend), * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$.

Table 30

Summary of Acrophases for Each Subject for all Study Variables in Whole Data Set Analysis and in Divided Data Analysis

Variable	Period (hr)	Subject	Whole Data Set	Segment A	Segment B
HR	24	1	18 hr, 33 min ± 1 hr, 26 min	18 hr, 47 min ± 21 min	8 hr, 47 min ± 1 hr, 50 min
		2	21 hr, 8 min ± 1 hr, 3 min	17 hr, 46 min ± 26 min	2 hr, 36 min ± 52 min
		3	NS	22 hr, 56 min ± 41 min	9 hr, 33 min ± 25 min
		4	4 hr, 25 min ± 1 hr, 38 min	12 hr, 50 min ± 1, hr 7 min	2 hr, 38 min ± 20 min
		5	20 hr, 43 min ± 1 hr, 18 min	15 hr, 27 min ± 37 min	33 min ± 26 min
		6	16 min ± 56 min	20 hr, 39 min ± 43 min	3 hr, 29 min ± 32 min
HR	12	1	6 hr, 2 min ± 49 min & every 12 hr	2 hr, 30 min ± 32 min	5 hr, 13 min ± 35 min
		2	NS	3 hr, 52 min ± 38 min	NS
		3	NS	NS	NS
		4	NS	5 hr, 8 min ± 28 min	5 hr, 40 min ± 44 min
		5	6 hr, 12 min ± 20 min and & 12 hr	5 hr, 47 min ± 13 min	NS
		6	NS	NS	NS
HR	6	1	NS	4 hr, 43 min ± 13 min	NS
		2	NS	4 hr, 58 min ± 20 min	2 hr, 24 min ± 19 min
		3	NS	NS	1 hr, 25 min ± 22 min
		4	NS	1 hr, 53 min ± 11 min	NS
		5	NS	NS	2 hr, 31 min ± 15 min
		6	NS	NS	3 hr, 37 min ± 26 min
HR	4	1	3 hr, 13 min ± 13 min & every 4 hr	NS	3 hr, 9 min ± 5 min
		2	1 hr, 48 min ± 8 min & every 4 hr	NS	1 hr, 45 min ± 6 min
		3	NS	NS	NS
		4	NS	2 hr, 31 min ± 15 min	1 hr, 24 min ± 17 min
		5	NS	NS	NS
		6	NS	1 hr, 13 min ± 16 min	NS

table continues

Table 30 (continued)

Variable	Period (hr)	Subject	Whole Data Set	Segment A	Segment B
PACs	24	1	15 hr, 14 min ± 1 hr, 10 min	3 hr, 38 min ± 1 hr, 4 min	13 hr, 52 min ± 37 min
		2	NS		
		3	NS		
		6	None		
	4	1	3 hr, 46 min ± 17 min & every 4 hr	NS	3 hr, 51 min ± 17 min
		2	NS		
		3	NS		
		6	None		
AT	24	1	NS	NS	NS
		2	None		
		3	None		
		6	None		
	4	1	3 hr, 2 min ± 14 min & every 4 hr	NS	2 hr, 58 min ± 14 min
		2	None		
		3	None		
		6	None		
PVCs	24	1	NS	NS	4 hr, 30 min ± 1 hr, 16 min
		2	NS	NS	NS
		3	9 hr, 39 min ± 1 hr, 42 min	NS	NS
		6	2 hr, 13 min ± 42 min	3 hr, 14 min ± 1 hr 22 min	1 hr, 49 min ± 46 min
	4	1	2 hr, 59 min ± 8.5 min & every 4 hr	21 min ± 13 min	2 hr, 56 min ± 7 min
		2	59 min ± 15 min & every 4 hr	NS	56 min ± 13 min
		3	3 hr, 36 min ± 14 min & every 4 hr	3 hr, 39 min ± 16 min	NS
		6	1 hr, 52 min ± 12 min & every 4 hr	1 hr, 45 min ± 13 min	NS
VCoup	24	1	23 hr ± 59 min	NS	23 hr, 36 min ± 1 hr, 3 min
		2	None		
		3	None		
		6	23 hr, 58 min ± 58 min	NS	1 hr, 19 min ± 1 hr, 1 min
	4	1	NS	1 hr, 24 min ± 17 min	NS
		2	None		
		3	None		
		6	NS		
VT	24	1	NS		
		2	None		
		3	None		
		6	NS		
	4	1	NS		
		2	None		
		3	None		
		6	NS		

HR, heart rate; PACs, premature atrial contractions; AT, atrial tachycardia; PVCs, premature ventricular contractions; and NS, nonsignificant.

Note: Acrophases are expressed in hours after customary midsleep.

Within Segment A, Subject 1 had significant 24-hour rhythms in heart rate and PACs; and a 12-hour rhythm and a 6-hour rhythm in heart rate (Table 31).

Within Segment B Subject 1 had significant 24-hour rhythms in heart rate, PACs, PVCs, and ventricular couplets; a 12-hour rhythm in heart rate; and 4-hour rhythms in heart rate, PACs, atrial tachycardia, PVCs, and ventricular couplets. Generally, mesors, amplitudes, and acrophases differed between segments and acrophases were generally nonoverlapping within segments. The 24-hour heart rate rhythm acrophases occurred within the expected time range.

Within Segment A, Subject 2 had significant 24-hour rhythms. 12-hour rhythms, and 6-hour rhythms in heart rate (Table 32). Within Segment B, 24-hour rhythms and 6-hour rhythms were found in heart rate. Four-hour rhythms were found in heart rate and PVCs. Generally, mesors, amplitudes, and acrophases differed between segments and acrophases were generally nonoverlapping within segments. In Segment A, acrophase in the 24-hour rhythm of heart rate occurred when expected.

Within Segment A, Subject 3 had a significant 24-hour rhythm in heart rate and a 4-hour rhythm in PVCs (Table 33). Within Segment B, she had a significant 24-hour rhythm and 6-hour rhythm in heart rate. As seen in previously discussed subjects, rhythm characteristics differed between and within segments. The acrophase in the 24-hour rhythm in heart rate occurred when expected in Segment B. She also had significant 24-hour rhythms in stroke volume and cardiac output with acrophases occurring when expected.

Subject 4 had a significant 24-hour, 12-hour, and 4-hour rhythms in

Table 31

Significant Rhythms and Acrophases for All Study Variables in Divided Data Analysis for Subject 1

Period (hr)	Variable	Acrophase (A)	Acrophase (B)
24	HR	18 hr, 47 min ± 21 min	8 hr, 47 min ± 1 hr, 50 min
	PACs	3 hr, 38 min ± 1 hr 4 min	13 hr, 52 min ± 37 min
	PVCs	-----	4 hr, 30 min ± 1 hr, 16 min
	VCoup	-----	23 hr, 36 min ± 1 hr, 3 min
12	HR	2 hr, 30 min ± 32 min	5 hr, 13 min ± 35 min
		14 hr, 30 min ± 32 min	17 hr, 13 min ± 35 min
6	HR	4 hr, 43 min ± 13 min	-----
		10 hr, 43 min ± 13 min	-----
		16 hr, 43 min ± 13 min	-----
		22 hr, 43 min ± 13 min	-----
4	HR	-----	3 hr, 9 min ± 5 min
		-----	7 hr, 9 min ± 5 min
		-----	11 hr, 9 min ± 5 min
		-----	15 hr, 9 min ± 5 min
		-----	19 hr, 9 min ± 5 min
		-----	23 hr, 9 min ± 5 min
	PACs	-----	3 hr, 51 min ± 17 min
		-----	7 hr, 51 min ± 17 min
		-----	11 hr, 51 min ± 17 min
		-----	15 hr, 51 min ± 17 min
		-----	19 hr, 51 min ± 17 min
		-----	23 hr, 51 min ± 17 min
	AT	-----	2 hr, 58 min ± 14 min
		-----	6 hr, 58 min ± 14 min
		-----	10 hr, 58 min ± 14 min
		-----	14 hr, 58 min ± 14 min
		-----	18 hr, 58 min ± 14 min
		-----	22 hr, 58 min ± 14 min
	PVCs	21 min ± 13 min	2 hr, 56 min ± 7 min
		4 hr, 21 min ± 13 min	6 hr, 56 min ± 7 min
		8 hr, 21 min ± 13 min	10 hr, 56 min ± 7 min
		12 hr, 21 min ± 13 min	14 hr, 56 min ± 7 min
		16 hr, 21 min ± 13 min	18 hr, 56 min ± 7 min
		20 hr, 21 min ± 13 min	22 hr, 56 min ± 7 min
	VCoup	1 hr, 24 min ± 17 min	-----
		5 hr, 24 min ± 17 min	-----
		9 hr, 24 min ± 17 min	-----
		13 hr, 24 min ± 17 min	-----
		17 hr, 24 min ± 17 min	-----
		21 hr, 24 min ± 17 min	-----

HR, heart rate; PACs, premature ventricular contractions; PVCs, premature ventricular contractions; VCoup, ventricular couplets; and AT, atrial tachycardia

Table 32

Significant Rhythms and Acrophases for All Study Variables in Divided Data Analysis for Subject 2

Period (hr)	Variable	Acrophase (A)	Acrophase (B)
24	HR	17 hr, 46 min ± 26 min	2 hr, 36 min ± 52 min
12	HR	3 hr, 52 min ± 38 min	-----
		15 hr, 52 min ± 38 min	-----
6	HR	4 hr, 43 min ± 20 min	2 hr, 24 min ± 19 min
		10 hr, 43 min ± 20 min	8 hr, 24 min ± 19 min
		16 hr, 43 min ± 20 min	14 hr, 24 min ± 19 min
		24 hr, 43 min ± 20 min	20 hr, 24 min ± 19 min
4	HR	-----	3 hr, 9 min ± 5 min
		-----	7 hr, 9 min ± 5 min
		-----	11 hr, 9 min ± 5 min
		-----	15 hr, 9 min ± 5 min
		-----	19 hr, 9 min ± 5 min
		-----	23 hr, 9 min ± 5 min
	PVCs	-----	56 min ± 13 min
		-----	4 hr, 56 min ± 13 min
		-----	8 hr, 56 min ± 13 min
		-----	12 hr, 56 min ± 13 min
		-----	16 hr, 56 min ± 13 min
		-----	20 hr, 56 min ± 13 min

HR, heart rate; PVCs, premature ventricular contraction

Table 33

Significant Rhythms and Acrophases for All Study Variables in Divided Data Analysis for Subjects 3 and 4

Subject	Period (hr)	Variable	Acrophase (A)	Acrophase (B)
3	24	HR	22 hr, 56 min ± 41 min	9 hr, 33 min ± 25 min
	6	HR	-----	1 hr, 25 min ± 22 min
			-----	7 hr, 25 min ± 22 min
			-----	13 hr, 25 min ± 22 min
			-----	19 hr, 25 min ± 22 min
	4	PVCs	3 hr, 39 min ± 16 min	-----
			7 hr, 39 min ± 16 min	-----
			11 hr, 39 min ± 16 min	-----
			15 hr, 39 min ± 16 min	-----
			19 hr, 39 min ± 16 min	-----
			23 hr, 39 min ± 16 min	-----
4	24	HR	12 hr, 50 min ± 1 hr, 4 min	2 hr, 38 min ± 20 min
	12	HR	5 hr, 8 min ± 28 min	5 hr, 40 min ± 44 min
			17 hr, 8 min ± 28 min	17 hr, 40 min ± 44 min
	6	HR	1 hr, 53 min ± 11 min	-----
			7 hr, 53 min ± 11 min	-----
			13 hr, 53 min ± 11 min	-----
			19 hr, 53 min ± 11 min	-----
	4	HR	2 hr, 31 min ± 15 min	1 hr, 24 min ± 17 min
			6 hr, 31 min ± 15 min	5 hr, 24 min ± 17 min
			10 hr, 31 min ± 15 min	9 hr, 24 min ± 17 min
			14 hr, 31 min ± 15 min	13 hr, 24 min ± 17 min
			18 hr, 31 min ± 15 min	17 hr, 24 min ± 17 min
			22 hr, 31 min ± 15 min	21 hr, 24 min ± 17 min

HR, heart rate; PVCs, premature ventricular contractions

heart rate in both segments (Table 33). In Segment A only, he had a 6-hour rhythm in heart rate only. The acrophases in the 12-hour rhythms in heart rate overlapped between segments. The 24-hour heart rate acrophase in Segment A occurred when expected.

Subject 5 had significant 24-hour rhythms in heart rate, cardiac output, and stroke volume. Within Segment A, he had significant 24-hour and 12-hour rhythms in heart rate; within Segment B, significant 24-hour rhythm characteristics differed between segments. The 24-hour heart rate acrophase occurred when expected in Segment A only (Table 34). Cardiac output and stroke volume acrophases did not occur when exptected.

Within Segment A, Subject 6 had significant 24-hour rhythms in heart rate and PVCs and 4-hour rhythms in heart rate, PVCs, and ventricular couplets. Within Segment B, he had significant 24-hour rhythms in heart rate, ventricular couplets, and PVCs; 6-hour rhythm in heart rate; and 4-hour rhythms in PVCs and ventricular couplets (Table 34). Rhythm characteristics differed between segments. Acrophases did not occur when expected.

Summary

Heart Rate Rhythms

Cosinor analysis of the whole heart rate data set revealed significant 24-hour rhythms ($p<0.056$; R^2 3.1%-8.8%) in all but one subject. Because of the difference in overall heart rate between study day one and study day two, individual data were divided into two segments (generally based on time of extubation) and cosinor analysis repeated on each segment (segments did not always have exactly 24 hours

Table 34

Significant Rhythms and Acrophases for All Study Variables in Divided Data Analysis for Subjects 5 and 6

Subject	Period (hr)	Variable	Acrophase (A)	Acrophase (B)
5	24	HR	15 hr, 27 min ± 37 min	33 min ± 26 min
	12	HR	5 hr, 47 min ± 13 min	-----
			17 hr, 47 min ± 13 min	-----
	6	HR	-----	2 hr, 31 min ± 15 min
			-----	8 hr, 31 min ± 15 min
			-----	14 hr, 31 min ± 15 min
			-----	20 hr, 31 min ± 15 min
6	24	HR	20 hr, 39 min ± 43 min	3 hr, 29 min ± 32 min
		PVCs	3 hr, 14 min ± 1 hr, 22 min	1 hr, 49 min ± 46 min
		VCoup	-----	23 hr, 31 min ± 1 hr, 3 min
	6	HR	-----	3 hr, 37 min ± 26 min
			-----	9 hr, 37 min ± 26 min
			-----	15 hr, 37 min ± 26 min
			-----	21 hr, 37 min ± 26 min
	4	HR	1 hr, 13 min ± 16 min	-----
			5 hr, 13 min ± 16 min	-----
			9 hr, 13 min ± 16 min	-----
			13 hr, 13 min ± 16 min	-----
			17 hr, 13 min ± 16 min	-----
			21 hr, 13 min ± 16 min	-----
		PVCs	1 hr, 45 min ± 13 min	-----
			5 hr, 45 min ± 13 min	-----
			9 hr, 45 min ± 13 min	-----
			13 hr, 45 min ± 13 min	-----
			17 hr, 45 min ± 13 min	-----
			21 hr, 45 min ± 13 min	
		VCoup	-----	1 hr, 19 min ± 1 hr, 1 min
			-----	5 hr, 19 min ± 1 hr, 1 min
			-----	9 hr, 19 min ± 1 hr, 1 min
			-----	13 hr, 19 min ± 1 hr, 1 min
			-----	17 hr, 19 min ± 1 hr, 1 min
			-----	21 hr, 19 min ± 1 hr, 1 min

HR, heart rate; PVCs, premature ventricular contractions; VCoup, ventricular couplets

of data). Significant 24-hour rhythms of moderate amplitude were found in all subjects for both segments (n=5, p<0.006, R^2=11.6%-67%; n=1, p<0.09, R^2 4.7-52.8%). Repeat analysis of the first 24 hours of data revealed significant 24-hour rhythms of moderate amplitude in all subjects (p<0.001).

In the whole heart rate data set, 24-hour acrophases overlapped in Subjects 2 and 5 and occurred when expected in normals (9.75-18.75 hours after midsleep) in Subject 1. In Segment A, no 24-hour acrophases overlapped. In Segment A, Subjects 1, 2, 4, and 5 had acrophases when expected. In Segment B, Subjects 2, 4, and 6 had overlapping acrophases and Subjects 1 and 3 had overlapping acrophases. Subject 1 and 3 had acrophases during the expected time interval for normals.

Twenty four-hour acrophases between Segments A and B were not similar. Acrophases in the whole data set overlapped with divided data set on two occasions: Subject 1, whole set and Segment A; Subject 4, whole set and Segment B.

Significant 12-hour rhythm of moderate amplitude were found in the whole heart rate data set in Subjects 1 and 5 (p<0.058; R^2 3.1%-15.9%). When divided data were analyzed, significant 12-hour rhythms of moderate amplitude were found in both segments in two subjects (Subject 1, p<0.01; R^2=9.4-12.6%; Subject 4, p<0.05, R^2=6.5%-14.9%); and in Segment A only in two subjects (Subject 2, p<0.001, R^2=12.7%; Subject 5, p<0.001, R^2=46.3%).

In the whole data set, acrophases for the 12-hour rhythms overlapped between Subjects 1 and 5. One of Subjects 1's 12-hour-rhythm acrophase overlapped with his 24-hour-rhythm acrophase. In Segment A,

12-hour-rhythm acrophases overlapped in Subjects 4 and 5; in Segment B, overlap was found in Subjects 1 and 4.

When 12-hour acrophases were compared within subject, agreement between analyses varied. For Subject 1, there was agreement between acrophases in the whole data set and Segment B. For Subject 4, Segments A and B had overlapping acrophases. For Subject 5, acrophases in the whole data set and acrophases in Segment A overlapped.

No significant 6-hour rhythms were found in the whole heart rate data set. In the divided data analysis, 6-hour rhythms of moderate amplitude were found in Segment A in only Subjects 1 and 4; in Segment B only in Subjects 3, 5, and 6; or in both segments in Subject 2 ($p \leq 0.079$; R^2 6.1%-23.8%). Acrophases within Segment A overlapped in Subjects 1 and 2. Acrophases within Segment B overlapped in Subjects 2 and 4.

Significant 4-hour rhythms of moderate amplitude in heart rate were found in two subjects (Subject 1, $p=0.014$; R^2 4.5%; Subject 2, $p=0.000$, $R^2=11.8\%$). When divided data were analyzed, only Segment B had significant 4-hour rhythm in Subjects 1 and 2 ($p \leq 0.001$). Significant 4-hour rhythms were also found in both Segments A and B for Subject 4 ($p \leq 0.072$; $R^2=5.4\%-7.0\%$) and in Segment A only for Subject 6 ($p=0.079$; $R^2=6.1\%$). Acrophases in the whole data did not overlap. In Segment A, acrophases were similar, but did not overlap. In Segment B, acrophases in Subjects 2 and 4 overlapped.

Arrhythmia Rhythms

Cosinor analysis of arrhythmias ($n=4$) revealed significant 24-hour rhythms in PACs in Subject 1 ($R^2=5.8\%$), PVCs in Subjects 3 and 6 ($R^2=3.2-16.1\%$), and ventricular couplets in Subjects 1 and 6 ($R^2=7.4\%$-

8.1%). In the divided data, 24-hour rhythms were found in PACs (both segments), PVCs (Subject 1 - Segment B only), PVCs (Subject 6 - both segments), and ventricular couplets (Subject 1 - Segment B only). In the whole data set, acrophases in ventricular couplets overlapped in Subjects 1 and 6. In Segment B, acrophases of the 24 hour rhythms in PVCs and ventricular couplets overlapped in Subject 6.

When 24-hour-rhythm acrophases in arrhythmias were compared across analyses, differences were found. In Subject 1, the PAC acrophases overlap between the whole data set and Segment B only. The PVC acrophases overlap between the whole data set and both segments in Subject 6 only. In Subjects 1 and 6, the ventricular couplet acrophases overlapped between the whole data set and Segment B.

Significant 4-hour rhythms were found in the whole data set in PACs in Subject 1 ($\underline{R}^2$=2.8%), atrial tachycardia in Subject 1 ($\underline{R}^2$=3.6%) and PVCs in Subjects 1, 2, 3, and 6 ($\underline{R}^2$=3.6-9.7%). In the divided data, 4-hour rhythms were found in PACs (Segment B only), atrial tachycardia (Segment B), PVCs (Subject 1 - both segments; Subjects 3 and 6 - Segment A only; Subject 2 - Segment B only), and ventricular couplets (Segment A only - Subject 1). In the whole data set, acrophases in the atrial arrhythmias in Subject 1 did not overlap. The PVC acrophases did not overlap ($\underline{n}$=4). In the divided analysis, acrophases within segments did not overlap. When 4-hour rhythm acrophases in arrhythmias are compared across analyses differences are found. The PAC acrophases overlapped between the whole data set and Segment B as did the acrophases in atrial tachycardia. In Subjects 1 and 2, the PVC acrophases overlapped between the whole data set and Segment B, and Subjects 3 and 6 had overlap

between the 4-hour rhythm PVC acrophases in the whole data set and Segment A.

Cardiac Output and Stroke Volume Rhythms

A significant 24-hour rhythm was found in cardiac output in two subjects (Subject 3, $p=0.006$, $R^2=45.6\%$; Subject 5 $p=0.056$, $R^2=33.7\%$). Mesors and amplitudes were similar. Acrophases did not overlap and only Subject 3 had an acrophase during the expected time interval for normals. No 12-hour-rhythms were found in these two subjects and no 4-hour-rhythms were found in any of the subjects.

A significant 24-hour rhythm in stroke volume was found in the same two subjects that had significant 24-hour rhythms in cardiac output (Subject 3 $p\leq0.001$, $R^2=63\%$; Subject 5 $p=0.096$, $R^2=28.4\%$). Mesor and amplitude were higher for Subject 3 than for Subject 5; acrophases between subjects did not overlap. Only Subject 3's acrophase occurred during the expected time interval for normals. Acrophases in cardiac output and stroke volume overlapped within subject. No 4-hour rhythms in stroke volume were found in any of the subjects.

CHAPTER V

DISCUSSION

The purpose of this study was to describe the temporal pattern of heart rate and rhythm, stroke volume, and cardiac output in critically ill adults in a cardiac surgical intensive care unit. This chapter discusses the results, including the effects of respiratory therapy, relationship of findings to customary midsleep, differences found between the three types of analyses (whole data set, Segments A and B, and first 24 hours of data), clinical significance of rhythms found, and patient profiles. Also included are the limitations of the study, recommendations for further study, conclusions, and implications for nursing practice and research.

Discussion of Results

Graphic analysis of data revealed much fluctuation in the measured variables. This finding was not surprising if one considered the physiologic adaptation occurring in the immediate postoperative phase after cardiac surgery. Cardiovascular variables were greatly influenced by this adaptation. Events that appeared to increase heart rate, the occurrence of arrhythmias, stroke volume, and cardiac output were: respiratory therapy (chest physiotherapy with and without inhalation of a bronchodilator), suctioning, position change, bathing, having catheters discontinued, vomiting, and shivering. These same events are also influencing the determinants of stroke volume and cardiac output: preload, afterload, and myocardial contractility.

Effects of Respiratory Therapy

Respiratory therapy was started postextubation on study day 2 in

five of the six subjects. Therapy was usually repeated every 4 hours and was consistently related to a clinically significant increase in heart rate (10 beats/min) in all five of the subjects. In those whose heart rate returned to pretherapy levels before the next treatment, it took a mean time of 1 hr, 45 min $\pm$ 52 min for the heart rate to return to pretherapy levels. Some heart rates did not return to pretherapy level during the observation period. Those subjects that had chest physiotherapy without a bronchodilator had a smaller increase in heart rate with a faster return to pretreatment levels. For those who had metaproterenol without chest physiotherapy, heart rates increased markedly and did not return to pretherapy levels during the observation period.

In the three subjects who had 4-hour heart rate rhythms in Segment B, acrophases occurred within approximately one hour of the initiation of respiratory therapy. Two of these subjects did not have a significant 4-hour rhythm in Segment A of the data when no respiratory therapy was given. Thus, the 4-hour rhythmicity seen was probably due to respiratory therapy.

For the four subjects with arrhythmias (PACs, atrial tachycardia, PVCs, ventricular tachycardia), these events increased in frequency with respiratory therapy except for one treatment in Subject 2, when the bronchodilator was albuterol instead of the usual metaproterenol. Two of these four, Subjects 1 and 2, had significant 4-hour rhythms in arrhythmias in Segment B only and the acrophases followed the time of initiation of respiratory therapy. The other two subjects, 3 and 6 did not have significant 4-hour rhythms in PVCs in Segment B but did in

Segment A. Subject 3 did not have respiratory therapy and Subject 6 had respiratory therapy late in the data collection period. Thus the 4-hour rhythmicity seen in the occurrence of arrhythmias was also probably due to respiratory therapy.

In the study hospital, respiratory therapy was routinely begun post extubation on all adult patients who had had cardiac surgery. All subjects responded to respiratory therapy with an increase in heart rate (range of increase was from 4 to 29 beats/min). An increase in heart rate increases the myocardial oxygen need. In addition, an increase in heart rate reduces diastolic filling time in the ventricles, resulting in decreased coronary artery filling. Cardiac surgical patients have a delicate balance between myocardial oxygen need and myocardial oxygen supply. The increased incidence in arrhythmias seen in this study may indicate a deterioration of this balance.

The effects of chest physiotherapy, including inhalation of bronchodilators, need to be evaluated further in critically ill patients. The routine use of this therapy is questionable in patients who have good respiratory function preoperatively and who will be intubated for only a short time as is common in patients having cardiac surgery. Clinically, cardiac surgical patient responses to respiratory therapy need to be monitored closely and therapy changed or stopped if important changes in heart rate or in the occurrence of arrhythmias are seen.

Relationship of Findings to Customary Prehospital Midsleep

In this study, acrophases of cardiovascular variables (expressed as hours after customary prehospital midsleep) did not always occur when

expected, based on research on healthy subjects presented earlier. Acrophases varied, depending on whether all data were analyzed or whether divided data were analyzed. For example, 24-hour-rhythm acrophases in heart rate occurred when expected only in Subject 1 when the whole data set was analyzed. When 24-hour-rhythm heart rate data were divided into two segments, four subjects had acrophases when expected in Segment A, but only two subjects had acrophases when expected in Segment B.

In the whole data set, acrophases for the 24-hour rhythms of arrhythmias were variable. The acrophases for PACs (n=1) occurred when expected; but the acrophases for ventricular couplets (n=2) did not. The acrophase for PVCs occurred when expected in one subject, but not in another. In the divided arrhythmia data, acrophases between segments were different for PACs and PVCs and did not occur when expected except for one PAC 24-hour acrophase in Subject 1 in Segment B. The acrophases of cardiac output and stroke volume occurred when expected in Subject 3 and did not in Subject 5.

Acrophases may have occurred at unexpected times because of all the biological noise in the data. Many treatments and environmental variables were simultaneously affecting the measured variables in these critically ill adults. For example, respiratory therapy clearly affected heart rate and rhythm and may have masked or altered acrophases of these variables. Other causes of altered acrophases may be true dysynchrony in circadian rhythmicity due to the effects of anesthesia or other medications, surgery, hypothermia, or the ICU environment. It is interesting to note that in Segment A, more subjects

had heart rate acrophases when expected, than in Segment B. The strong influence of the respiratory therapy in Segment B may be partially responsible for this finding. Additionally dysynchrony, if occurring, may not be apparent immediately in the postoperative period. Subject 3, who was the only woman in this study and the only one who was in the hospital for two weeks prior to surgery, did not have a 24-hour heart rate acrophase when expected in Segment A but did in Segment B. She did have 24-hour cardiac output and stroke volume acrophases when expected. She did not receive respiratory therapy during this study and she may have still been adjusting to the ever-changing hospital time schedule during the two study days. Subject 1, who was the only subject to have 24-hour heart rate acrophases when expected in both segments, was the only subject who did not have CABG surgery. This finding suggests that those with CHD who have had CABG surgery may have different acrophases from those with valvular heart disease who have had valve surgery. Clinically, one might expect acrophases to vary from normal in those who have had CABG surgery and to vary from normal more on postoperative day 2 or 3 than on postoperative day 1. Further study is needed to describe acrophases in different postoperative days in different groups of patients.

Differences between the Findings in Segments A and B

Heart rate was higher during Segment B than in Segment A in all but one subject who was receiving intravenous isoproterenol during Segment A. Isoproterenol is a beta-1 agonist and causes an increase in heart rate. Differences were found in periods and acrophases in heart rate and arrhythmias between Segment A and B and may reflect the fact that

over 48 hours, patients were changing in response to their environment and therapy. During the first study day, patients were intubated and were recovering from general anesthesia, cardiac surgery, hypothermia, and being on the heart-lung machine. By the second study day, patients were awake, usually extubated and participating in care, visiting with family and friends, having catheters and tubes discontinued, being weaned off intravenous vasoactive medications, and generally being disturbed. Also, respiratory therapy was begun on study day two in all but one subject. Thus, study days 1 and 2 were very different both physiologically and environmentally for these cardiac patients. In spite of these differences, it is noteworthy that 24-hour rhythms of heart rate could still be detected in both segments in all subjects. Rhythm characteristics were different from day to day, either due to the masking effects of biological noise or due to actual change in the rhythm. More 24-hour heart rate acrophases occurred when expected in Segment A than in Segment B. Acrophases occurred later in Segment A than in Segment B. Nurses should be aware that the period of overt rhythms and acrophases may be shifting from day to day within the individual and that changes seen in these variables clinically may be due to changes in the endogenous rhythm. For a specific patient the exact fluctuation is unknown, and confounds interpretation of values obtained in these variables. But knowing that fluctuations are expected adds some explanatory value in understanding changes seen.

Differences between Findings of Segment A and First 24 Hours of Data

Because data split based on time of extubation did not always allow for a complete 24 hours of data in the analysis, cosinor analysis was

repeated on the first 24 hours of heart rate data for each subject. Subjects 1, 2, and 4 had differences in periods and acrophases between the two analyses, while Subjects 3, 5, and 6 did not. For Subjects 1, 2, and 4, Segment A included 18.25-22.75 hours of data and this meant that in the first 24 hours of data analysis, 1.25-5.75 hours of data were added. These added hours of data included the addition of data that were occurring during the first respiratory therapy session. For Subjects 3, 5, and 6 this was not the case. For Subject 3, respiratory therapy was not started during the first 24 hours so the addition of 5.75 hours to Segment A did not seem to affect findings. For Subjects 5 and 6, Segment A contained 24.75-25.5 hours of data. Thus, differences seen in Subjects 1, 2, and 4 were probably due to the addition of data that were affected by respiratory therapy.

Even though Segment A sometimes had less than 24 hours of data, rhythm analysis of this segment was probably more indicative of the actual patient state prior to extubation (Segment A) than analysis of the first 24 hours of data. Adding hours of data postextubation to complete a 24-hour set of data, may have distorted the rhythm analysis by including post-extubation data. Post-extubation data generally had a higher mean heart rate and were influenced by the every 4 hour respiratory therapy. Clinical criteria, like the ones used in this study, need to be generated and used to make decisions as to how to divide data for accurate rhythm analysis.

Differences between Findings of Whole Data Set and Segments

Findings between the analyses of the whole data set and of the segments were different. For example, even though a 24-hour rhythm in

heart rate could be detected in both analyses, the mesors, amplitudes, and acrophases were different. Use of segmented data to describe the rhythmic properties of the study variables in these critically ill adults seems appropriate. The patient situations were different between the two study days; therefore, the data need separate description. These separate descriptions of temporal patterns are necessary to provide useful data to understand changes seen clinically in these variables. When data from different patient states are combined, findings can be nonspecific and in fact misleading.

For future biological rhythm research with critically ill patients, segmental analysis of data that are collected over days is recommended. Data could be divided into 24 hour days or divided based on events such as extubation and the beginning of respiratory therapy that seem to be markers of change in the variable. This type of analysis would provide information about day-to-day changes in rhythm characteristics of these variables in these ill adults. Knowing the expected day-to-day changes in rhythm characteristics would be useful to nurses caring for these patients as they interpret patients' vital signs and plan care.

Heart Rate Rhythms

Mesors in the whole data set ranged from 88-119 beats/min. In the divided data set, mesors ranged from 78-123 beats/min. These heart rates are within the range commonly found in critically ill adults. The rhythms found in the whole data set had half-amplitudes of 2-4 beats/min (peak to trough amplitude of 4-8 beats/min). The divided data had half-amplitudes of 2-8 beats/min (peak to trough amplitudes of 4-16 beats/min). These changes are clinically important. Acrophases

(in hours after customary midsleep) in the 24-hour rhythms for Segment A ranged from 12 hr, 50 min ± 1 hr, 7 min to 22 hr, 56 min ± 41 min; in Segment B they occurred earlier and ranged from 33 min ± 26 min to 9 hr, 33 min ± 25 min.

Only one previous study (Leach et al., 1983) could be found that examined rhythmicity of heart rate in a patient after cardiac surgery. The subject, a man who was in coma for ten days following surgery, had a 24-hour rhythm in heart rate. A 96-hour rhythm and a 7-day rhythm also were found. Acrophases and mesors were not reported.

Patients with myocardial infarction in cardiac care units (CCUs) have been found by several investigators to have 24-hour rhythms of moderate amplitude in heart rate (Kuzel, 1973; Dominichelli et al., 1980; Morrison et al., 1981; and Carpeggiani et al., 1987). Kuzel (1973) found various ultradian (16 hr, 8 hr, 4.8 hr, 2.82 hr, 1.41 hr) rhythms in these patients. In all these studies, means or mesors ranged from 64-97 beats per minute. Mesors of heart rate in this study were higher (Segment A, 83-116 beats/min; Segment B, 78-122 beats/min). Acrophases or peaks occurred at various times in the day, for example 0100-1525 (Kuzel, 1973), 1731 (1628-1840)(Domenichelli et al., 1980), and 1200-1800 (Morrison et al., 1981). Carpeggiani and coworkers found peaks during the activity period. None of these studies referenced peaks or acrophases to actual sleep time or reported customary sleep time. Thus, comparison of acrophases between studies was difficult. If one assumed that midsleep in these studies was 0300, then the findings in Segment A of this study were similar to those of Kuzel and Domenichelli and coworkers.

Felver and Hoeksel (1990) found significant 24-hour heart rate rhythms of moderate amplitude in seven of eight medical ICU patients ($p<0.085$). Similar rhythms were found in this study. In Felver and Hoeksel's study explained variance ranged from 4.6%-48.0% and half-amplitude ranged from 1 $\pm$ 0.5 to 10 $\pm$ 1 beat/min. Two pairs of subjects had overlapping acrophases and three subjects had acrophases during the expected time period (9.75-18.75 hours after midsleep). Significant 12-hour rhythms were also found in six subjects ($p<0.09$). Explained variance ranged from 4.5%-16.4%. Half-amplitude ranged from 1 $\pm$ 0.5 to 5 $\pm$ 1 beats/min. Three pairs of subjects had overlapping acrophases. Five subjects had significant 6-hour rhythms in heart rate ($p<0.044$) and explained variances ranged from 6.1%-45%. Half-amplitude ranged from 3 $\pm$ 1 to 6 $\pm$ 1 beats/min. Acrophases were almost identical in one pair of subjects and overlapped in another pair. One subject was found to have a significant 4-hour rhythm.

A summary of periods found in both studies follows:

	24-hr	12-hr	6-hr	4-hr
Felver & Hoeksel ($N=8$)	$n=7$	$n=6$	$n=5$	$n=1$
Woods ($N=6$)				
Whole data set	$n=5$	$n=2$	$n=0$	$n=2$
Segment A	$N=6$	$n=4$	$n=3$	$n=2$
Segment B	$N=6$	$n=2$	$n=4$	$n=3$

Felver and Hoeksel found more 12-hour and 6-hour rhythms than the current study did, but the current study found more 4-hour rhythms. In some cases, these 4-hour rhythms in this study were related to respiratory therapy. More subjects in ICUs need to be studied before conclusions can be made, but it appears that both ultradian and circadian rhythms in heart rate are occurring simultaneously, helping to explain the variability seen in these cardiovascular variables.

Acrophases for the 24-hour rhythms in heart rate (in hours after customary midsleep) were variable in both studies:

	Range of Acrophases ± 1 SE
Felver and Hoeksel	31 min ± 1 hr, 45 min to 14 hr, 49 min ± 30 min
Woods (whole data)	16 min ± 56 min to 21 hr, 8 min ± 1 hr, 3 min
Woods (Segment A)	12 hr, 50 min ± 1 hr, 7 min to 22 hr, 56 min ± 41 min
Woods (Segment B)	2 hr, 36 min ± 52 min to 9 hr, 33 min ± 25 min

Some of these acrophases in both studies occurred when expected (9.75-18.75 hours after midsleep), while others did not. Felver and Hoeksel found three of their seven subjects to have acrophases when expected. In Segment A, Subjects 1, 2, 4, and 5 had acrophases when expected and in Segment B only Subjects 1 and 3.

Both these studies had small numbers of subjects. More ICU patients need to be studied to describe further the temporal pattern in heart rate. The expected range of heart rate for ICU patients may be different from what is expected in normal subjects and needs to be described in different patient groups. With this range described, then these variables measured clinically can be compared with known baseline fluctuation.

Finding variable acrophases is not surprising when one considers the ICU environment and the patient's ever-changing physiologic condition. Heart rate is highly affected by exogenous stimuli, as are all the determinants of stroke volume: preload, afterload, and contractility. Patients are probably in the midst of reentraining and adapting to the new environment while they are critically ill. Additionally, this environment is changing from day to day as the patient's condition changes. In the current study, acrophases and mesors were changing from one day to the next day. Knowing that heart

rate is fluctuating in overall mean from day-to-day and that the incidence of arrhythmias is peaking earlier than expected on postoperative days 2 and 3 provides the clinician with information that aids in interpreting heart rate and rhythm changes seen in these patients.

Arrhythmia Rhythms

Four of six subjects had enough arrhythmias for meaningful analysis. Findings between segments were sometimes different. For Subject 1, 24-hour rhythms in PACs were found in both segments, but the 24-hour rhythm in PVCs was found only in Segment B. Four-hour rhythms of PACs and atrial tachycardia were found only in Segment B. The 4-hour rhythm of PVCs was found in both segments, but the explained variance in Segment B was higher than in Segment A. Respiratory therapy was given in Segment B and this therapy was related to the 4-hour rhythms in arrhythmias found in Segment B. Subject 2 had a 4-hour rhythm of low amplitude in PVCs in Segment B only. He also had respiratory therapy during Segment B. Subject 3 had a 4-hour rhythm of low amplitude in Segment A. Subject 6 had 24-hour rhythm of moderate amplitude in PVCs in both segments and had a 4-hour rhythm of moderate-amplitude in PVCs in Segment A. He also had a 24-hour rhythm of low-amplitude in ventricular couplets in Segment B and a 4-hour rhythm of low amplitude in ventricular couplets in Segment A.

Any arrhythmia in a critically ill patient who has questionable myocardial oxygen supply and demand balance, is clinically important. In addition, many of the cardiac patients also have electrolyte imbalances, impaired gas exchange, and fluid volume excess which

predispose them to arrhythmias. If peak times of incidence of arrhythmias are known, then interventions could be timed to reduce the occurrence of arrhythmias. Acrophases in this study were variable. In the whole data set, the 24-hour acrophase for these four subjects for all arrhythmias ranged widely from 2 hr, 13 min ± 42 min to 23 hr, 58 min ± 58 min after customary midsleep. For Segment A, acrophase ranged from 3 hr, 14 min ± 1 hr, 22 min to 3 hr, 38 min ± 1 hr, 4 min; for Segment B, acrophases ranged from 4 hr, 30 min ± 1 hr, 16 min to 23 hr, 36 min ± 1 hr, 3 min.

Leach and coworkers found in one patient in coma for 10 days after cardiac surgery, a 24-hour rhythm in runs of PVCs but isolated PVCs did not have a 24-hour rhythm. Mesors and acrophases were not reported, which precluded comparison with this study. No other study of temporal patterns in arrhythmias in patients in ICU could be found.

Kuzel (1973) studied patients with myocardial infarction in the CCU and found circadian and ultradian rhythms in PACs and PVCs, and junctional escape beats. Acrophases for the 24-hour rhythms in PACs were 0728-1845; in PVCs were 0743-1820. Customary sleep time was not reported. If one assumed that midsleep was 0300, then the acrophase for PACs and PVCs were similar to those found in Segment B of this study. The CCU provides a quieter environment than the ICU.

Other studies of cardiac patients have found circadian rhythms in PVCs (Orth-Gomer et al., 1982; DeSalzi et al., 1984; DeLeonardis et al., 1985; Calfiero et al., 1986; Tammaro et al., 1986; Rossi et al., 1986; & Biffi et al., 1987). As in Segment B of this study, acrophases for these arrhythmias were variable ranging throughout the day and night.

Ultradian rhythms in PVCs have been found, as well (DeSalzi et al., 1984; & DeLeonardis et al., 1984). Ventricular tachycardia was found to have a circadian rhythm with acrophases ranging from 1102-1429 (Rebuzzi et al., 1987; Lucente et al., 1988). Two subjects in this study had ventricular tachycardia without evidence of a circadian or ultradian rhythm. PACs have also been found to have circadian and ultradian rhythms (DeSalzi et al., 1984; DeLeonardis et al., 1985; Rossi et al., 1986). The current study also found 24-hour rhythms in PACs, PVCs, and ventricular couplets; and 4-hour rhythms in PACs, atrial tachycardia, PVCs, and ventricular couplets. Knowing the temporal characteristics of arrhythmia occurrence in specific types of patients provides a rationale for timing nursing interventions. More subjects need to be studied to describe these temporal characteristics and to identify patient characteristics that will enable nurses to predict patterns.

Rhythms of Cardiac Output and Stroke Volume

Two of the six subjects in this study had 24-hour rhythms in cardiac output and stroke volume. Mesors for cardiac output ranged from 6.3 $\pm$ 0.22 to 6.57 $\pm$ 0.13 l/min; for stroke volume ranged from 53.7 $\pm$ 0.78 to 64.3 $\pm$ 1.32 ml/beat. These averages are within the normal range and are commonly seen in cardiac surgical patients. Half-amplitude for cardiac output ranged from 0.7 $\pm$ 0.2 to 0.8 $\pm$ 0.3 l/min; for stroke volume ranged from 5.9 $\pm$ 2.6 to 9.89 $\pm$ 1.8 ml/beat. These differences are clinically important and could influence treatment decisions. As expected, acrophases were overlapping between cardiac output and stroke volume, within each subject, but were not between subjects. These acrophases were very different from the heart rate acrophases found.

Thus the rhythms found in cardiac output were not driven by the rhythms in heart rate. No 4-hour or 12-hour (in the two subjects that had significant 24-hour rhythms) rhythms of cardiac output and stroke volume were found.

No previous study of temporal patterns in cardiac output and stroke volume could be found that included acutely ill hospitalized patients. Adamian and coworkers (1984) found significant ($p<0.05$) 24-hour rhythms of low amplitude in cardiac output and stroke volume in a hospital setting in 141 subjects (cardiac patients, $n=115$; normals, $n=26$). Cardiac output mesors for the cardiac patients ranged from 3.2-3.3 l/min, stroke volume mesors ranged from 43.1-46.6 ml/beat. Both these mesors were lower than those found in this study. Half-amplitudes for cardiac output ranged from 0.26-0.31 l/min, and for stroke volume ranged from 2.6-3.2 ml/beat. These amplitudes were less than found in this study. Acrophases for cardiac output ranged from 1309-1632 and for stroke volume 1252-1345 (all slept from 2230 to 0730). These acrophases, when referenced to midsleep (0300), overlapped with one subject in the current study (#3). Differences found in mesor, amplitude, and acrophases between the current study and the study by Adamian are probably due to the different environments and acuity of illness studied.

Miller and Helander (1979) also found 24-hour rhythms of moderate amplitude in cardiac output and stroke volume in two healthy, day-active males aged 33 and 34 years. Measurements were made hourly for 48 hours. Mesors for cardiac output were 5.56 ± 0.35 and 7.19 ± 0.72 l/min; for stroke volume were 90 ± 7 and 155 ± 13.2 ml/beat. These were wider

ranges than seen in the subjects of the current study. Half-amplitudes of cardiac output rhythms were from 0.37 and 0.54 l/min; for stroke volume rhythms 3.9 and 9.3 ml/beat. Larger amplitudes were found in the current study. Acrophases for cardiac output were 2012 and 2254; for stroke volume were 0048 and 0430. The acrophases of Subject 5 in the current study overlapped with the acrophases of one subject in Miller and Helander's study. Differences found between the two studies were probably due to the types of subjects (normals and critically ill adults) and environments studied.

F. Halberg (1983) found in one day-active person a significant 24-hour rhythm in cardiac output and stroke volume. Acrophases ranged from 1430-1445 and were similar to the acrophase found in Subject 3 of this study (1448 $\pm$ 1 hr). No other data or methods were presented.

Thus, there is agreement that some normal subjects and non-hospitalized cardiac patients have 24-hour rhythms in cardiac output and stroke volume as did two of the six subjects in this study. Mesors, amplitudes, and acrophases were variable, with some overlap between subjects. Acrophases for normal subjects and patients need further description in order to understand the endogenous fluctuation seen clinically in cardiac output and stroke volume.

Patient Profiles

All six subjects were studied in the immediate postoperative period following cardiac surgery. Only one subject did not have CABG surgery (#1) and only one subject was a woman (#3). Four were between the ages of 33-43 years and two were between the ages of 67-68 years. Only one subject normally slept between 0400 and 1000 (#6). The first five

subjects were studied in January or February and the last subject was studied in June. Three subjects had diabetes mellitus (#3, #5, and #6).

Subject 1 had 24-hour rhythms in heart rate, PACs, and ventricular couplets with nonoverlapping acrophases. He had a 12-hour rhythm in heart rate and one of the acrophases overlapped with the 24-hour rhythm acrophase of heart rate. Four-hour rhythms in heart rate and PACs were found. When data were divided, 24-hour rhythms were found in heart rate (both segments), PACs (both segments), PVCs (Segment B only) and ventricular couples (Segment B only). The 12-hour rhythm in heart rate continued in both segments. Mesor was higher in Segment B and acrophases were non overlapping. The 4-hour rhythms were found in heart rate (Segment B only), PACs (Segment B only), and atrial tachycardia (Segment B only). Segments A and B had different mesors and acrophases for heart rate. The rhythmicity seen in Segment B was related to the effects of respiratory therapy. All acrophases in the 4-hour rhythms were related to the timing of respiratory therapy.

Subject 2, had 24-hour rhythm in heart rate and 4-hour rhythms in heart rate and PVCs. Acrophases were similar but did not overlap. When data were divided, 24-hour rhythms were found in heart rate (both segments). The 4-hour rhythm of heart rate and PVCs were found in Segment B only. Again the time of respiratory therapy coincided with the acrophases of the 4-hour rhythm. Segments A and B had similar mesors in heart rate but acrophases were different. Six-hour rhythms in heart rate were found in both segments with differing acrophases.

Subject 3 had 24-hour rhythms in PVCs, cardiac output, and stroke volume. All had overlapping acrophases. Four-hour rhythms were found

in PVCs and one of the acrophases overlapped with the 24-hour acrophases. When heart rate data were divided, 24-hour rhythms of moderate amplitude were found in both segments. Acrophases were very different which helps to explain why a 24-hour rhythm in heart rate was not detected in the whole data set. A 6-hour rhythm in heart rate was found in Segment B only. A 4-hour rhythm was found in PVCs in Segment A only. Although, Subject 3 did not have respiratory therapy, the differences found between segments suggests that the two study days were different.

Subject 4 had a 24-hour rhythm in heart rate. When data were divided, 4-hour, 12-hour, and 24-hour rhythms were found in both segments. Acrophases for the 4-hour rhythms were nonoverlapping; for the 12-hour rhythms were overlapping; and for the 24-hour rhythms were not overlapping. Mesors were very different between segments. A 6-hour rhythm in heart rate was found in Segment B only. Respiratory therapy was given every 4 hours during study day 2 and acrophases coincided with the time of respiratory therapy. Again study day 1 was different from study day 2.

Subject 5 had 24-hour rhythms in heart rate, cardiac output, and stroke volume and acrophases overlapped. Heart rate also had a 12-hour rhythm with one of the acrophases overlapping with the 24-hour rhythm acrophase in heart rate. When heart rate data were divided, 24-hour rhythms were found in both segments, with differing mesors and acrophases. A 12-hour rhythm was found in Segment A only and a 6-hour rhythm in Segment B only. Again, study day 1 was different from study day 2.

Subject 6 had 24-hour rhythms in heart rate, PVCs, and ventricular couplets with differing acrophases. There was a 4-hour rhythm in PVCs. When data were divided, the 24-hour rhythms in heart rate and PVCs continued. Acrophases for heart rate in the two segments were different; acrophases for PVCs were overlapping. Ventricular couplets was found to have a 24-hour rhythm of low amplitude in Segment B only. The 4-hour rhythms of PVCs were found in Segment A only and ventricular couplets in Segment A only. Thus, study day 1 was different for study day 2 even though he did not receive respiratory therapy until the end of study day 2. Subject 6 was different from the other five subjects in that he usually slept from 0400 to 1000. All others went to sleep between 2200-2400. His data were also collected in June and the others' data were collected January through March. The small amplitude increase in heart rate that occurs in the summer was not observed in this subject.

Various pairs of subjects had overlapping acrophases in some variables and periods but not in others. Subjects 2 and 4 had overlapping heart rate acrophases more than once (for 24-hr, 6-hr, 4-hr rhythm Segment B). Both of these subjects had respiratory therapy in Segment B. Subjects 1 and 3 had overlapping 24-hour rhythm heart rate acrophases in Segment B and very similar 4-hour rhythm acrophases in PVCs in the whole data set. Subjects 1 and 2 had similar 24-hour rhythm acrophase in heart rate, and overlapping 6-hour rhythm acrophases in heart rate in Segment A. Both of these subjects had respiratory therapy in Segment B. Although, there were these similarities, there was still much variation in this group of patients and this study was not designed

to identify related characteristics.

Limitations of the Study

This study was limited by the small sample size (N=6) which restricted the representativeness of the sample. Only four of the six subjects had arrhythmias, thus limiting generalizability of the arrhythmia findings. Circadian and ultradian rhythms in selected arrhythmias could be identified; this finding lends credence to the need for further description of temporal patterns in arrhythmias in critically ill adults. In addition, subjects' ages ranged from 33-43 years (n=4) and 67-68 years (n=2) and only one woman was included. However, all subjects were the same in that they had had a cardiac surgical procedure and were in the immediate recovery period. Findings cannot be extended to other populations.

Study data were collected over 48-hour periods by two individuals each working 12-hour shifts. Both investigators found the data collection to be extremely fatiguing, especially when two subjects were studied one after the other. The detailed protocol for data collection and the tape-recorded heart rate and rhythm data helped to counteract the effects of fatigue in this study. Fatigue could have inadvertently affected the accuracy of recorded information.

Because of difficulty in finding eligible subjects who met the study inclusion criteria, data collection occurred through winter (n=5) and spring (n=1). The difficulty was due primarily to the fluctuations in the number of adult cardiac surgeries in the ICU and because of the inconsistent use of pulmonary artery catheters. It is known that there can be small seasonal effects on amplitudes of the variables measured,

but these effects were not seen in this study.

Another problem inherent in studying variables that require invasive catheters that are only placed by a physician is that nurse investigators are dependent on the physician's judgment as to when catheters are placed and discontinued. Some subjects had their pulmonary artery catheters discontinued prior to 48 hours of data collection. Thus, usable data for cardiac output and stroke volume ranged from 25 to 45.75 hours.

In the study ICU the usual procedure for thermodilution cardiac output measurement limits the number of injections of 5 ml iced-injectate in a single measurement to two. The surgeon in charge of the unit indicated that this was an attempt to restrict fluid in these cardiac patients but gave permission to use a third 5 ml injection for the purpose of this study. Occasionally, the three cardiac output values obtained were not within 10% of each other. When the nurse in charge of the patient judged that the patient was in no danger of fluid overload, a fourth or sometimes a fifth injection was made. The fluid received was recorded on the patient's chart and the hourly intravenous fluid was adjusted accordingly. At times when fluid overload was a problem, the three cardiac output values obtained were averaged. In no case was the variation 15% above or 15% below the middle value.

Areas for Further Study

To improve the generalizability of the findings of this study, more subjects need to be studied. Further description of the temporal pattern in cardiovascular variables is needed. Thus, replication of this study in a cardiac surgical ICU with a larger number of subjects is

needed. It is recommended that data analysis include cosinor analysis of divided data as was done in this study. Critically ill patients are different physiologically from day to day and rhythm in this study characteristics were changing. Also, further study is needed in other types of patient groups and settings: other surgical ICUs and medical ICUs.

Whether the temporal patterns seen postoperatively in this study were the same as the subject's usual prehospital patterns is unknown. This study found that rhythm characteristics were different between study days. Treatments and environmental factors were different between days and are certainly different from a usual prehospital experience. Usual sleep patterns are greatly disrupted. Further study is needed to compare prehospital temporal patterns in heart rate and rhythm with postoperative temporal patterns in the hospital and after discharge.

Further study is also needed to describe the temporal patterns in the determinants of stroke volume (preload, afterload, and contractility) in cardiac surgical ICU patients. Knowledge of these temporal patterns would provide a basis for understanding the rhythm characteristics seen in stroke volume and cardiac output.

Factors that cause disruption in patients' circadian rhythms when they are placed in an ICU need to be described. Nursing interventions could eventually be described that would promote maintenance of circadian rhythmicity of cardiovascular variables.

Significance and
Implications for Nursing Practice and Research

This study is the first to describe the temporal patterns in heart

rate and rhythm, stroke volume, and cardiac output in critically ill adults in a cardiac surgical ICU. This study is the first to use thermodilution cardiac output measurements to describe the temporal pattern in cardiac output and stroke volume and the first study to measure heart rate and rhythm, stroke volume, and cardiac output simultaneously.

The study found clinically significant circadian and ultradian rhythms in heart rate and rhythm, and circadian rhythms in cardiac output and stroke volume in some critically ill patients in a cardiac, surgical ICU. Subjects were in the immediate postoperative period following cardiac surgery and their conditions were unstable. They were receiving numerous medications and were in a disruptive ICU environment. Even in this environment with unstable conditions, low-to-moderate amplitude rhythms in these variable were detected, although rhythm characteristics changed from day one to day two.

Knowing that these rhythmic variations are occurring in these patients adds explanatory value in understanding changes in heart rate and rhythm, stroke volume, and cardiac output. For example, if one knew in a specific patient when a trough in cardiac output was expected, then when this decrease was observed one might understand that the decrease did not necessarily mean an adverse change in heart function. Even if one did not know a specific patient's rhythm characteristics, knowledge that these rhythms continue in critically ill adults may provide an explanation for fluctuations in vital signs seen clinically. For a given individual, therapy or interventions should be timed to coincide with a person's periods of physiological susceptibility and periods of

physiological resistance. Thus, these periods need description if nursing interventions are to be timed appropriately. For example, if arrhythmias occur at a specific time of day, a nurse could monitor more closely and administer antiarrhythmic medications at a time to ensure adequate blood levels during this peak time of incidence.

For research, these findings demonstrate the need to incorporate segmental analysis of data collected over days in critically ill adults. The patient's condition and environment are ever-changing and the overt rhythms of these variables are changing from day to day. Rhythms with these amplitudes could confound findings of research that uses these variables as outcome variables, if circadian variation is not considered. Generally in this study, peaks in heart rate, arrhythmias, cardiac output, and stroke volume occurred during the customary activity period and troughs occurred during customary sleep. Studies should be designed to consider subjects' customary sleep/wake cycle and include time of customary sleep as an inclusion criterion. The length of a research study during a 24-hour period should be limited when possible to time within sleep or the activity period, avoiding known time periods of increasing or decreasing values.

This is the first study to describe the temporal patterns of heart rate and rhythm, stroke volume, and cardiac output simultaneously measured in critically ill adults in a cardiac surgical ICU. Knowledge that rhythms are occurring and that their characteristics are changing from day to day adds some explanatory value in understanding why changes in these variables may be seen clinically and in research settings.

Further research building on this study is feasible and necessary since it is possible to detect rhythmicity in the overt data of these critically ill people. This area of research could ultimately improve patient care.

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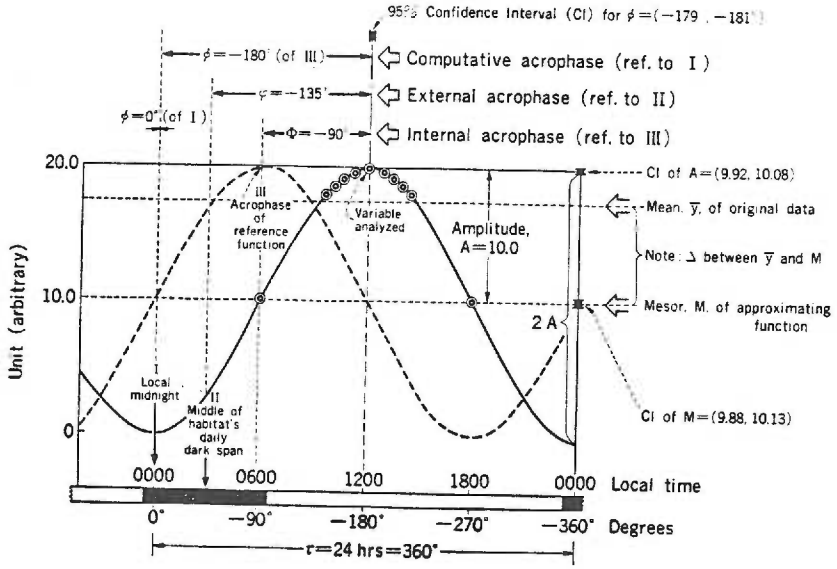
Appendix A

Glossary of Chronobiologic Terms

acrophase - "measure of timing; the lag from a defined reference timepoint of the crest time in the function appropriately approximating a rhythm" (Halberg, Caradente, Cornelissen, Katinas, 1977, p. 16). "There are three types of acrophases: computative, external and internal. (See figure below from Halberg & Lee, 1974, p. xxxvii.)

Units: Angular: degree, radian.
Time: second, minute, hour, day month, year.
Episodal: integer (such as number of heart beats)"
(Halberg, & Lee, 1974, p xxxvii).

SCHEME OF QUANTITATIVE RHYTHM CHARACTERISTICS



"Rhythm characteristics obtained by the least squares fit of a single cosine curve: the mesor, which can be different from the sample mean in the case of unequidistant data; the amplitude and the extent of total change predictable by the fit of a single cosine curve, namely the double amplitude. Different types of acrophase estimates depend upon the reference point chosen as zero time in estimating the lag of the crest time in the cosine curve approximating all data: (a) the computative acrophase referred to some computationally convenient reference such as midnight local time--on day I of studies on

circadian rhythms (or on December 22 of previous year, for the case of circannual rhythms, etc.), (b) the external acrophase referred to a point on some environmental cycle such as the midpoint of the dark-span (in one's bedroom or habitat niche) when living on a 24-hr cycle of light and darkness or (c) the internal acrophase referred to the peak of another cosine curve approximating another physiologic series used as the reference series." (Halberg & Lee, 1974, p. xxxviii)

amplitude - "difference between maximum and mesor of a best fitting cosine" (Halberg et al., 1977, p. 26).
"Units: Original physiologic units, e.g., number of heart beats, mm Hg in blood pressure, etc." (Halberg & Lee, 1974, p. xxxvii).

angular frequency - "(ω) special case of frequency corresponding to the number of repetitions of a periodic process in a unit of time, e.g., ω in y_i=M + A cos (ωt_i + ϕ) + e_i, where M=mesor, A=amplitude, ϕ=acrophase and t_i=time. Relation: $\omega=2\pi/\tau=2\pi f$, since frequency, $f=1/\tau$ (period). Units: Degrees (or radians) per unit time." (Halberg & Lee, 1974, p. xxxvii)

autorhythmicity - self measurement (Minor & Waterhouse, 1981). Automatic recording of physiologic variables (Halberg & Lee, 1974).

biologic noise - "random or other (useless) components (of a signal), interfering with the (useful) part of the signal (e.g., rhythm) to be evaluated." (Halberg & Lee, 1974, p. xxxvii)

"Note: Biologic noise--from unidentified and identified sources, separately evaluated or unevaluated--can be computed as the variability remaining after the (e.g., least squares) fit of a model used for approximating a rhythm. In this sense, noise equals the error term in a statistical model and the relative contribution of noise as interference with the predictable (and thus useful) part of the signal is described as Percent Error" (Halberg & Lee, 1974, p. xxxvii).

biorhythm - "rhythm persisting as a fundamental property of biologic entities under various conditions of presumed constancy in environmental factors (including those possibly known to synchronize the rhythm)" (Halberg & Lee, 1974, p. xxxviii).

chronobiologic window - "print-out or graphic display of results obtained by least squares fitting of cosines, usually display of amplitudes and percent errors at chosen trial periods" (Halberg & Lee, 1974, p. xxxviii).

chronobiology - "science objectively quantifying and investigating mechanisms of biologic time structure, including rhythmic manifestations of life" (Halberg, et al., 1977, p. 50).

chronobiologic serial section - "analytical results obtained by fitting a fixed-period cosine curve to consecutive overlapping or non-overlapping data sections, called intervals, displaced in increments throughout a time series--displayed with the original data as 'moving' P values (for rhythm description) as moving point and interval estimates for mesor, amplitude and acrophase of a rhythm" (Halberg & Lee, 1974, p. xxxix).

chronodesm - "time-qualified reference interval, e.g., time-qualified prediction or tolerance interval" (Halberg, et al., 1977, p. 52).

chronogram - "individual or averaged display of data as a function of time for macroscopic viewing" (Halberg & Lee, 1974, p. xxxix).

circadian - "relating to biologic variations or rhythms with a frequency of 1 cycle in 24 ± 4 hr; circa (about, approximately) and dies (day or 24 hr)" (Halberg, et al., 1977, p. 67).

circadiseptan - "relating to biologic variations or rhythms with a frequency of 1 cycle in 14 ± 3 days" (Halberg & Lee, 1974, p. xxxix).

circannual - "relating to biologic variations or rhythms with a frequency of 1 cycle in 1 year ± 2 months" (Halberg, et al., 1977, p. 68).

circaseptan - "relating to biologic variations or rhythms with a frequency of 1 cycle in 7 ± 3 days" (Halberg, et al., 1977, p. 69).

circatrigintan - "relating to biologic variations or rhythms with a frequency of 1 cycle in 30 ± 5 days" (Halberg, et al., 1977, p. 69).

circavigintan - "relating to biologic variations or rhythms with a frequency of 1 cycle in 21 ± days" (Halberg, et al., 1977, p. 69).

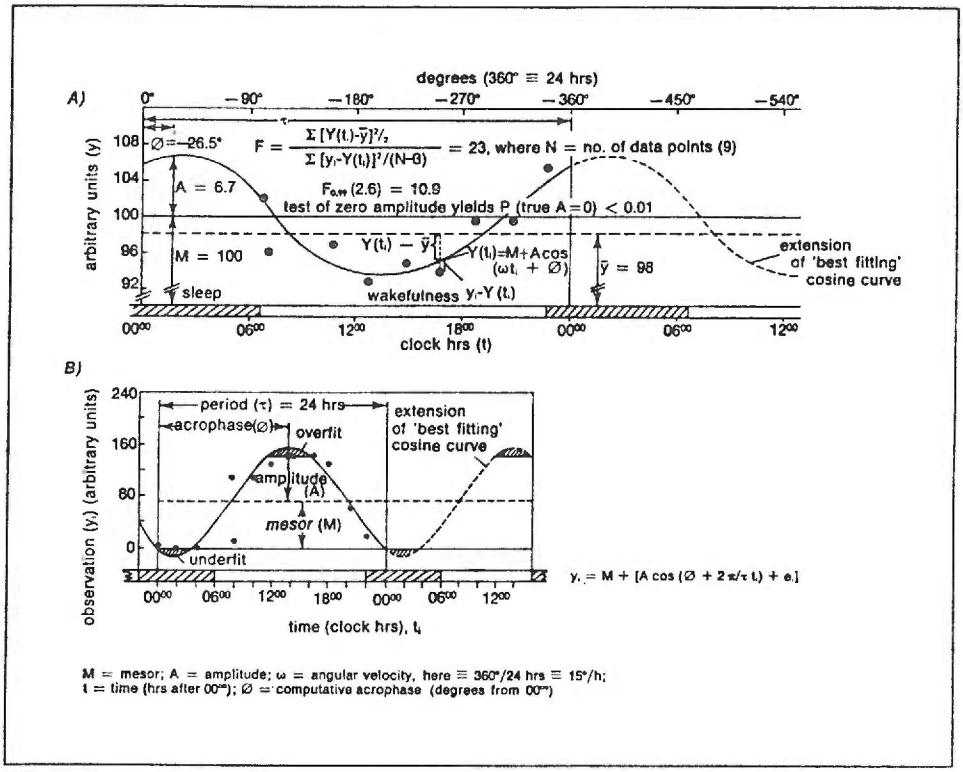
confidence interval - "inferential statistical interval for a single parameter investigated." (Halberg & Lee, 1974, p. xli)

"Note: If two estimates E_1 and E_2 of the lower and upper limits of the parameter E satisfy the relation $P(E_1<E<E_2)=1-\alpha$, where α is some fixed probability (e.g., 0.05), the interval between E_1 and E_2 is called (e.g., 95%) confidence interval for the unknown parameter E. The assertion that E lies in this interval will be true, on the average, in a proportion $1-\alpha$ of the sampling cases when the assertion is made. The values E_1 and E_2 are called the confidence limit." (Halberg & Lee, 1974, p. xli)

cosinor - "statistical summary with display on polar coordinates of a biologic rhythm's amplitude and acrophase relations by means of the length and angle of a directed line, respectively, shown with a bivariate statistical confidence region computed (at chosen trial period) 1) to detect a rhythm (by a confidence region not overlapping the pole), and 2) to estimate confidence intervals for the rhythm parameters" (Halberg, et al., 1977, p. 72).

"Note: Cosinor procedures are of several kinds:

Mean Cosinor, cosinor-M: the cosinor procedure applicable to 3 or more biologic series from an individual or a group. Inputs of cosinor-M are imputations consisting of amplitudes and acrophases from each individual series. Cosinor-M is applied when the mesors from individual series are different but the amplitudes are similar and the number of data points from each series is approximately equal. Single Cosinor, cosinor-S: a cosinor procedure applicable to single biologic time series or to a set of series (from an individual or group) which all have similar mesors and similar amplitudes. Number-Weighted Mean Cosinor (Ponderatus), cosinor-P: a cosinor procedure weighted with the number of observations in each series, applicable to 2 or more biologic series from one or more individuals when the mesors, amplitudes and particularly the number of data points in each series are quite different" (Halberg & Lee, 1974, p. xlii).



A) Testing rhythm sinusoidality by variance ratio, F;
abstract example with 24-h cosine function y(t), continuous curve, fitted by least squares to data $y_i(o)$ obtained during wakefulness span;
M = mesor; A = amplitude; ω = angular velocity, here ≡ 360°/24 hrs ≡ 15°/h; t = time (hrs after 00^m); Ø = computative acrophase (degrees from 00^m); ω = 2π/τ.

B) Parameter M, A and Ø estimation by least squares fit of cosine model with fixed period: $y_i = M + [A \cos (Ø + 2\pi/\tau t_i) + e_i]$;
t_i = time; y_i = observation at t_i; e_i = error at t_i, having an independent normal distribution with mean zero and unknown variance σ^2.

Computer programs facilitate inferential statistical rhythm detection in noisy data such as those usually collected in a clinic (*A*) and the estimation of the rhythm's properties (*B*).

desynchronization - "state of two or more previously synchronized rhythmic variables that have ceased to exhibit the same frequency and/or the same acrophase relationships and show changing time relations" (Halberg, et al., 1977, p. 79).

diurnal - "relating to biologic variations or events occurring between sunrise and sunset or during the illuminated fraction of a near-daily schedule of alternating artificial light and darkness" (Halberg, et al., 1977, p. 85).

entrainment - "interaction between two or more organismic macroscopic rhythms or the effect upon rhythm(s) of an (external) synchronizer resulting in identical frequencies among interactions or in frequencies constituting integral multiples of one another" (Halberg, et al., 1977, p. 89).

external desynchronization - "desynchronization of a biologic rhythm from an environmental cycle" (Halberg, et al., 1977, p. 92).

Fourier analysis - "study of representing functions of a time series as a combination of trigonometric functions, e.g., $F(t_i) = \sum_{j=1}^{p} \cos [\phi_j + (2\pi / \tau_j) t_i] i=1, \ldots, n$ where p is the number of cosine terms, ϕ_j the acrophases, τ_j the periods, t_i the time and $F(t_i)$ the representative function." (Halberg & Lee, 1974, p. xliii)

> "Note: Method more general than harmonic analysis." (Halberg & Lee, 1974, p. xliii)

free-running - "continuance of bioperiodicity with a natural frequency usually at least slightly different from any known environmental schedule" (Halberg, et al., 1977, p. 93)

frequency (f) - "the number of occurrences of a given type of event or the number of members of a population falling into a specified class. In a study of periodicity it is the number of cycles occurring per unit time, i.e., f is the reciprocal of the period (τ), $f=1/\tau$. (Halberg & Lee, 1974, p. xliii)

harmonic analysis - "study of function approximating a time series as a combination of trigonometric functions with periods in harmonic order, i.e., $F(t_i) = \sum_{j=1}^{p} \cos [\phi_j + (2 \pi j/\tau) t_i]$ where symbols are referred to Fourier Analysis." (Halberg & Lee, 1974, p. xliv)

imputation - "tentative estimation from limited or insufficient evidence, such as a procedure for deriving from a short time series endpoints used in further analyses such as a number-weighted or number-unweighted mean cosinor" (Halberg & Lee, 1974, p. xliv).

infradian - "relating to certain biologic variations or rhythms with a frequency lower-than-circadian" (less than 1 cycle in 28 hr)(Halberg, et al., 1977, p. 105).

internal desynchronization - "desynchronization from each other of two or more rhythms in the same entity by the appearance of a previously absent difference in frequency and/or a change in time relation... of two rhythms with the same frequency" (Halberg, et al., 1977, p. 108).

least-squares method - "estimation technique for determining quantities by minimizing the error (or residual) sum of squares. In a linear model, this method produces the best linear unbiased estimate in terms of variance" (Halberg, et al., 1977, p. 111).

linear least squares method - "least squares applied to a model linear in parameters". (Halberg & Lee, 1974, p. xlvi)

> "Note: The single cosine model $y_i = M + A \cos [\phi + (2 / \tau) t_i] + e_i$ is linear if the period is a priori fixed for analysis (whether or not it is known or unknown) in order to estimate the parameters M, A and ϕ" (Halberg & Lee, 1974, p. xlvi).

linear-nonlinear least squares method - "computational procedure for assessing sets of rhythm characteristics for several frequencies (unknown, unfixed) characterizing the data by applying first linear least squares followed by non-linear least squares" (Halberg & Lee, 1974, xlvi).

> "Note: LLS method provides a set of initial values for NLS which yield final results after an appropriate number of iterations" (Halberg & Lee, 1974, p. xlvi).

macroscopic (analysis) - "analysis based solely upon inspection of original data or of averages and dispersion indices plotted as a function of time" (Halberg & Lee, 1974, p. xlvi).

mesor - "rhythm-determined average, e.g., in the case of a single cosine approximation, the value midway between the highest and lowest values of function used to approximate a rhythm" (Halberg, et al., 1977, p. 126).

microscopic (analysis) - "analysis for detecting in a signal, e.g., in biologic time series (usually containing biologic noise) any temporal characteristic (useful part of a signal) and for obtaining objective numerical endpoints thereof" (Halberg & Lee, 1974, p. xlvi).

nocturnal - "relating to biologic variations or events occurring between sunset and sunrise or during dark fraction of a 24 hr schedule of alternating light and darkness" (Halberg, et al., 1977, p. 141).

nonlinear least squares method - "least squares method applied to a model nonlinear in parameters" (Halberg & Lee, 1974, p. xlvi).

> "Note: If the period is not fixed in a single cosine model (see LLS) this model is nonlinear and the period is a parameter. This model considers a set of parameters as a vector in 4 dimensions. For computation, one chooses a set of initial values--a vector--and moves this in parameter space by iteration guided by the principle of least squares. In Fourier's Analysis, NLS is needed for assessing several cosine terms, each with a set of 3 rhythm characteristics, in addition to the overall mesor" (Halberg & Lee, 1974, p. xlvi).

nychthemeral conditions - when normal periodicities of the solar day are present (Minor & Waterhouse, 1981).

period - (τ Greek, tau) "duration of one cycle in a rhythmic variation" (Halberg, et al., 1977, p. 150).

periodicity - "regularly repetitive change occurring in animate or inanimate nature, irrespective of inferential statistical considerations, waveform or of underlying mechanism" (Halberg, et al., 1977, p. 151).

periodogram - "display, as a function of an abscissa linear in period, of amplitude, residual error, variance or some other characteristic investigated by harmonic or other analysis" (Halberg & Lee, 1974, p. xlvii).

phase - "instantaneous state of a rhythm within a cycle" (Halberg & Lee, 1974, p. xlvii).

phase angle - "a time point in a periodicity considered in relation to another specified time point--acrophase and phase angle are interchangeable but acrophase or some comparable term defined as to zero phase is preferred to phase angle in chronobiology" (Halberg & Lee, 1974, p. xlvii).

phase-shift - "single abrupt or gradual displacement of a periodicity along the time scale" (Halberg & Lee, 1974, p. xlvii).

plexogram - "display of original data covering spans longer than the period of a rhythm investigated along a abscissa of a single period, irrespective of time order of collection, e.g., as a function of a single conventional or other time unit--such as a day, irrespective of calendar data and/or subject" (Halberg & Lee, 1974, p. xlvii).

rhythm - "a sequence of events that repeat themselves through time in the same order and at the same interval" (Minors & Waterhouse, 1981, p. 321).

rhythmometry - "detection of rhythm by inferential statistics and point-and-interval estimation of characteristics such as mesor, amplitude, acrophase, period (or frequency) and/or waveform" (Halberg & Lee, 1974, p. xlviii).

synchronization - "state of system when two or more variables exhibit periodicity with the same frequency and phase angle or with frequencies that are integer multiples or submultiples of one another" ((Halberg & Lee, 1974, p. xlviii).

synchronizer - "environmental periodicity determining the temporal placement of a given biologic rhythm along an appropriate time scale by impelling the rhythm to assume synchronization, i.e., its frequency or an integer multiple or submultiple of its frequency" (Halberg & Lee, 1974, p. xlviii).

> "Note: Also called Zeitgeber, time-giver, entraining agent, clue or cue" (Halberg & Lee, 1974, p. xlviii).

time series - (y_i, t_i): chronologic sequence of paired values, one of which is time, t_i the other a quantitative characteristic of an individual or population (y_i) at the time t_i" (Halberg & Lee, 1974, p. xlix).

> "Note: Biologic time series may consist of continuous, or discrete but equidistant or of unequidistant observations in time" (Halberg & Lee, 1974, xlix).

ultradian - "relating to biologic variations or rhythms with a frequency higher-than-circadian." (rhythms with frequencies greater than 1 cycle in 20 hr)(Halberg, et al., 1977, p. 185).

variation, coefficient of - "standard deviation of a distribution divided by the arithmetic mean (sometimes multiplies by 100)" (Halberg & Lee, 1974, p. L).

> "Unit: Dimensionless."
> "Note: Serves to compare variabilities of samples or populations and is independent of units and magnitudes of means, but is sensitive to errors in the means" (Halberg & Lee, 1974, p. L).

zeitgeber - "an external oscillation which is capable of entraining an endogenously generated biological rhythm" (Minor & Waterhouse, 1981, p. 321).

Appendix B

Electrocardiographic Characteristics of Arrhythmias

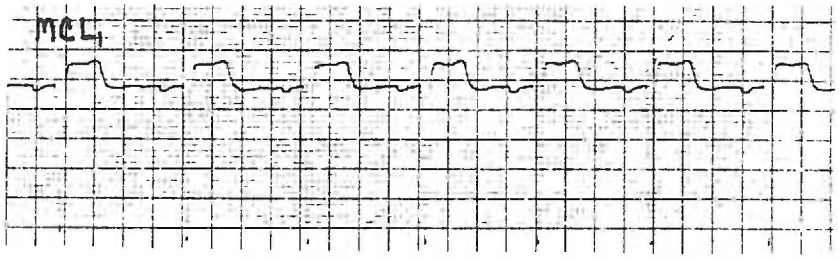
(Adapted from Woods, S.L. (1986). Arrhythmias and treatment, American Heart Association of Washington, Seattle, Washington)

Supraventricular Arrhythmias

I. Rhythm Originating in the Sinus Node

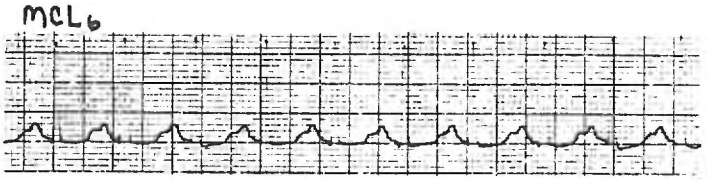
A. Normal Sinus Rhythm (NSR)

1. RATE: 60 to 100
2. P WAVES: Precede each QRS
3. PR INTERVAL: Normal, (0.12 sec. to 0.20 sec.). The upper limit of normal changes with heart rate.
4. QRS: Usually normal, (0.04 sec. to 0.10 sec.)
5. CONDUCTION: Conduction through the atria, AV node, and ventricles is usually normal.
6. RHYTHM: Regular
7. EXAMPLE:



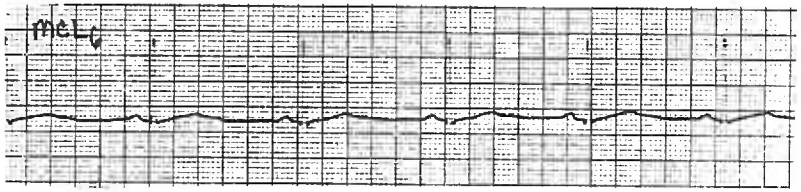
B. Sinus Tachycardia

1. RATE: 100 to 150
2. P WAVES: Precede each QRS. May be buried in the preceding T wave.
3. PR INTERVAL: Usually normal
4. QRS: Usually normal
5. CONDUCTION: Usually normal
6. RHYTHM: Regular
7. COMMENTS: All aspects of sinus tachycardia are the same as normal sinus rhythm except the rate is faster.
8. EXAMPLE:



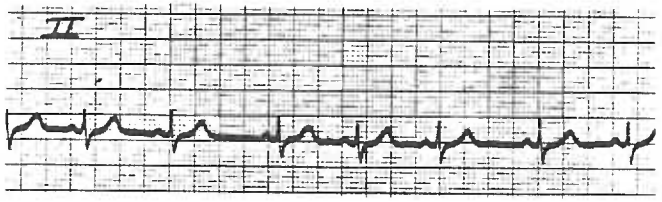
C. Sinus Bradycardia

1. RATE: 40 to 60
2. P WAVES: Precede each QRS
3. PR INTERVAL: Usually normal
4. QRS: Usually normal
5. CONDUCTION: Usually normal
6. RHYTHM: Regular
7. COMMENTS: All aspects of sinus bradycardia are the same as normal sinus rhythm except the rate is slower. The slow rate may be due to vagal stimulation. Remember that cardiac output = stroke volume x heart rate.
8. EXAMPLE:



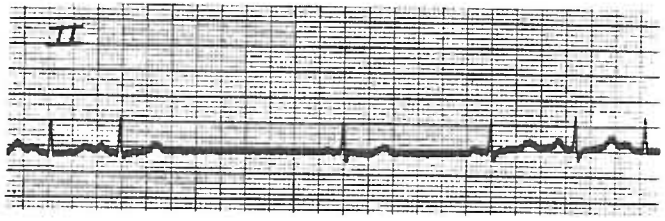
D. Sinus Arrhythmia

1. RATE: 60 to 100
2. P WAVES: Precede each QRS
3. PR INTERVAL: Normal
4. QRS: Usually normal
5. CONDUCTION: Usually normal
6. RHYTHM: May be related to breathing (rate increases with inspiration and decreases with expiration) or irregularity may be unrelated to respiration. The irregularity can best be seen by measuring the R-R interval.
7. COMMENTS: It is the most frequent form of arrhythmia and occurs as a normal phenomenon. Commonly occurs in the young or aged, especially with slower heart rates or following enhanced vagal tone from digitalis or morphine.
8. EXAMPLE:



E. Sinus Arrest

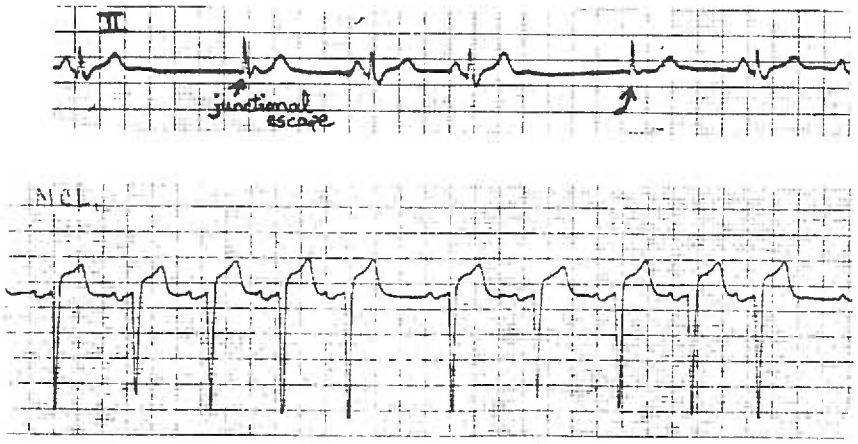
1. RATE: Usually 60 to 100, but frequently is less than 60.
2. P WAVES: P waves are intermittently absent resulting in a pause. If junctional escape beats occur, the P wave may be absent, may appear before the QRS complex, or may appear after the QRS complex.
3. PR INTERVAL: Usually normal
4. QRS: Usually normal
5. CONDUCTION: Usually normal
6. RHYTHM: Irregular. Junctional and ventricular escape beats may occur. The R-R intervals will be irregular.
7. COMMENTS: May occur following carotid sinus pressure. May be caused by vagal stimulation, sinus node disease, digitalis toxicity, and degenerative forms of fibrosis.
8. EXAMPLE:



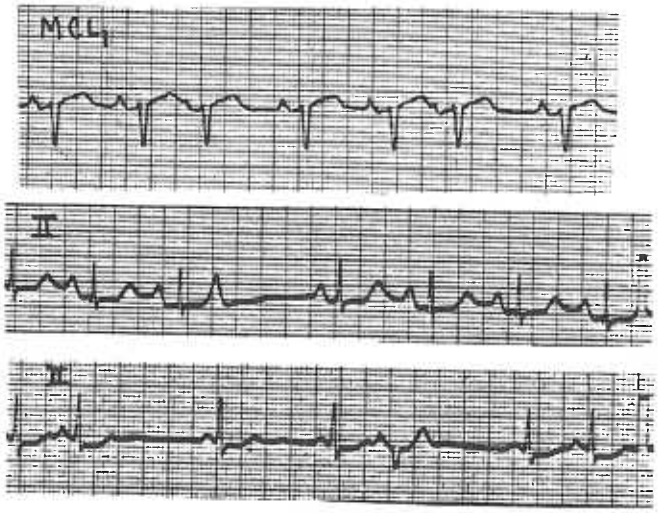
F. Sinus Atrial Block (Sinus Exit Block)

1. RATE: 60 to 100
2. P WAVES: Usually normal with occasional absent P waves.
3. PR INTERVAL: Usually normal. Will be absent when the P wave is absent.
4. QRS: Usually normal. Will be absent when the P wave is absent. Thus, a pause will be seen. The length of the pause is usually a multiple of the basic P-P interval, approximately 2, less commonly 3 or 4 times the normal P-P interval (Type II Exit Block).
5. CONDUCTION: Usually normal
6. RHYTHM: Irregular, due to the absent P wave and QRS complex.
7. COMMENTS: Type I (Wenckebach) sinus exit block may also occur, in which case the P-P interval progressively shortens (each delay is longer, but longer by less) prior to the pause and the duration of the pause is less than 2 P-P cycles. Digitalis produces Type II sinus exit block, but Type I heart block (Wenckebach). Sinus exit block may be caused by excessive vagal stimulation, by acute infections, by atherosclerosis involving the sinus nodal artery, or by fibrosis involving the atrium. Digitalis, quinidine, atropine, and salicylates all have been reported to cause sinus block.

8. EXAMPLE:



8. EXAMPLE:



II. Rhythms Originating in the Atria

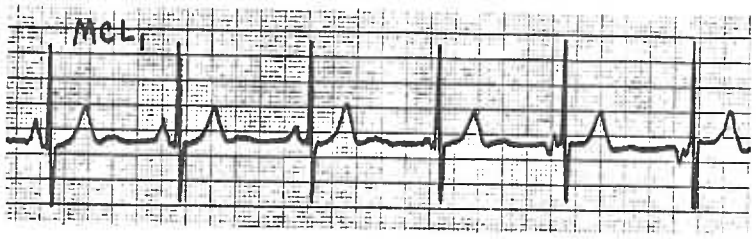
A. Premature Atrial Contraction (PAC)

1. RATE: 60 to 100
2. P WAVES: Usually have a different configuration than the P waves that have originated from the sinus node. Another site in the atria has become irritable and fired before the normal firing time of the sinus node.
3. PR INTERVAL: PR interval may vary from the PR intervals of impulses originating in the sinus node.
4. QRS: May be normal, aberrant, or absent. If the ventricles have completed their repolarization phase, they can respond to this early stimulus from the atria.
5. CONDUCTION: Usually normal
6. RHYTHM: Regular, except when the PACs occur. The P wave will be early in the cycle and usually will not have a complete compensatory pause. (Time between the preceding QRS complex and the following QRS complex is less than two normal R-R intervals.)
7. COMMENTS: Frequently seen in normal hearts. The patient may say that his heart skipped a beat. Caffeine, alcohol, or smoking may cause PACs.

B. Wandering Atrial Pacemaker

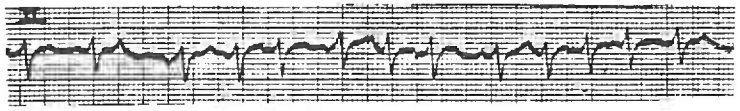
1. RATE: 60 to 100 (If rate is greater than 100, then it is called multifocal atrial tachycardia).
2. P WAVES: Impulse formation occurs anywhere from the sinus node to the AV node, thus the P wave will vary from impulse to impulse in size and configuration. Atrial rate is irregular. Stimulus coming from the sinus node or close to it will produce normal looking P waves. As the pacer wanders closer to the AV node, the P waves will become flatter or even inverted. At least three different P waves must be seen.
3. PR INTERVAL: The PR interval varies depending on the closeness of the pacemaker to the AV node.
4. QRS: Usually normal
5. CONDUCTION: Conduction from the AV node through the ventricles will usually be normal.
6. RHYTHM: The R-R intervals may vary due to variations in the PR intervals.
7. COMMENTS: The patient is usually unaware of this arrhythmia. It can only be documented by ECG. Sometimes it is associated with digitalis intoxication. Observe for other atrial arrhythmias.

8. EXAMPLE:



C. Multifocal Atrial Tachycardia

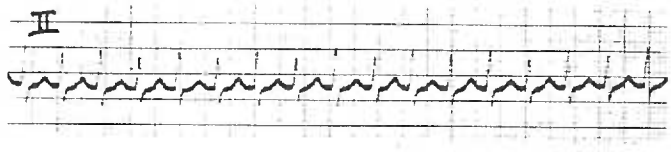
1. RATE: Above 100
2. P WAVES: Impulse formation occurs anywhere from the sinus node to the AV node. At least 3 different P waves are seen. The atrial rate is irregular.
3. PR INTERVAL: Varies with each complex.
4. QRS: Usually normal
5. CONDUCTION: Conduction from the AV node through the ventricles will usually be normal.
6. RHYTHM: The PR intervals may vary due to variations in the PR intervals.
7. COMMENTS: It is most commonly associated with severe pulmonary disease.
8. EXAMPLE:



D. Paroxysmal Atrial Tachycardia (PAT)

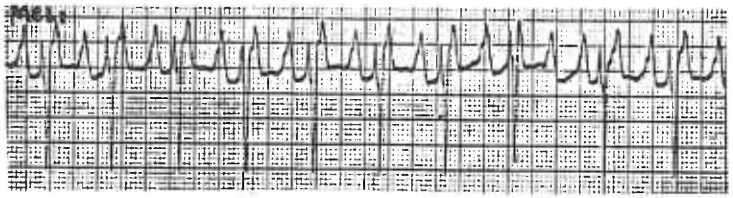
1. RATE: 150 to 250
2. P WAVES: Impulse formation originates somewhere in the atria other than the sinus node. Slightly to grossly abnormal. May be found in the preceding T wave.
3. PR INTERVAL: May be normal, prolonged, or shortened.
4. QRS: Usually normal
5. CONDUCTION: Usually normal
6. RHYTHM: Regular
7. COMMENTS: Characterized by abrupt onset and abrupt cessation. Abbreviated PAT. If the rhythm is not proxysmal, it is termed atrial tachycardia. Rhythm may be triggered by emotions, tobacco, caffeine, fatigue, sympathetic amines, or alcohol. Usually not associated with heart disease. Patient may not be aware of PAT. Rates between 140 to 160 could be either sinus tachycardia or PAT.

8. EXAMPLE:



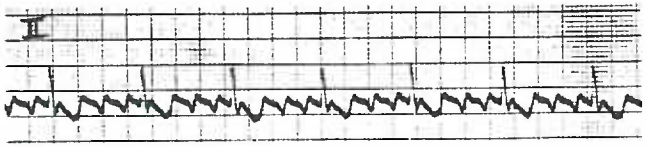
Paroxysmal Atrial Tachycardia (PAT) with Block

1. RATE: Atrial rate 150 to 250
2. P WAVES: Usually can be seen preceding each QRS; however, when block occurs, there will be a P wave that is not conducted to the ventricle. The P wave may be buried in the preceding T wave. The P wave will have different configuration than those from the sinus node. They frequently are smaller.
3. PR INTERVAL: May be normal, prolonged, or shortened.
4. QRS: Usually normal configuration and interval. The block may vary 2:1, 3:1, causing the ventricular rate to be irregular.
5. CONDUCTION: Many of the ectopic impulses from the atrium are blocked in the AV node; however, those that are conducted through the AV node usually have normal conduction through the ventricles.
6. RHYTHM: Usually regular
7. COMMENTS: Paroxysmal atrial tachycardia (PAT) is characterized by an abrupt onset. The rapid rate may produce angina due to decreased coronary artery filling. Cardiac output is decreased and heart failure can occur.
8. EXAMPLE:



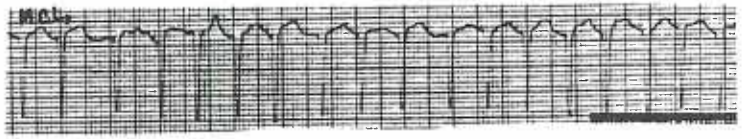
F. Atrial Flutter

1. RATE: Atrial rate 250 to 350. Most commonly 300. The ventricular rate will usually show some degree of block with the ventricles responding in a 2:1 or 4:1, rarely 3:1 pattern. There may be variations in the block pattern particularly if treatment has been started.
2. P WAVES: Characterized by the F waves occurring in a regular fashion and in a saw-tooth pattern. (Picket-fence pattern.)
3. PR INTERVAL: None
4. QRS: Usually normal
5. RHYTHM: Usually regular, but irregularities in the block pattern occur.
6. COMMENTS: Usually associated with heart disease, RHD, CHD, thyrotoxicosis, acute corpulmonale, heart failure, and myocardial infarction. Any ventricular response of 150 should be suspect for atrial flutter.
7. EXAMPLE:



G. Atrial Fibrillation

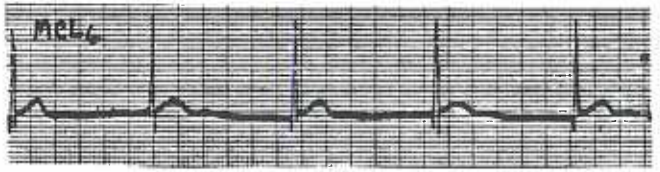
1. RATE: Atrial rate may be 350 to 600. Ventricular response is usually 120 to 200.
2. P WAVES: No discernable P waves. Irregular undulation termed "f waves" are seen.
3. PR INTERVAL: PR interval cannot be measured.
4. QRS: Usually normal
5. CONDUCTION: Usually normal through the ventricles. Characterized by an irregular ventricular response.
6. RHYTHM: Irregular and usually rapid unless controlled.
7. COMMENTS: A rapid ventricular response decreases ventricular filling time and thus the stroke volume. There is also the loss of the atrial kick, which is 25% to 30% of the cardiac output. Congestive heart failure frequently follows. Associated with heart failure, valvular heart disease, thyrotoxicosis, acute corpulmonale, and CHD. Coarse atrial fibrillation is more easily converted than fine atrial fibrillation.
8. EXAMPLE:



III. Rhythms Originating in the Junction

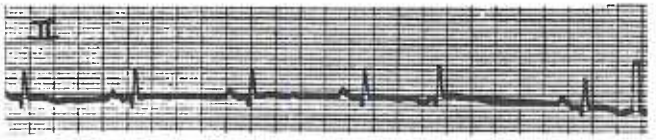
A. Junctional Rhythm

1. RATE: 40 to 60
2. P WAVES: They are usually inverted and may occur before, during, or after the QRS, depending on the speed of conduction in the junctional tissue. (Both antegrade and retrograde.)
3. PR INTERVAL: If the P wave occurs before the QRS, the PR interval is less than 0.12 second.
4. QRS: Usually normal
5. CONDUCTION: The atria are stimulated from the junctional tissue, resulting in an inverted P wave (called retrograde conduction). The conduction from the junctional tissue through the ventricles is usually normal.
6. RHYTHM: Regular
7. COMMENTS: Can only be differentiated from other bradycardia rhythms by ECG. May be from digitalis intoxication. Because the rate is so slow, other irritable sites may compete to be the dominant pacemaker.
8. EXAMPLE:



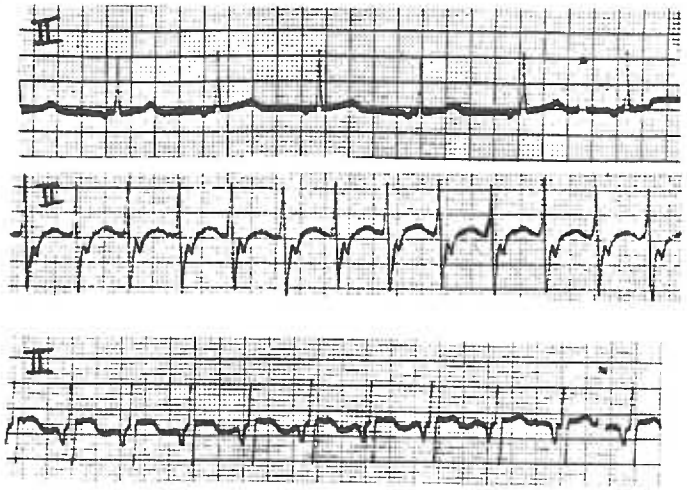
B. Premature Junctional Contraction (PJC)

1. RATE: 60 to 100 if the rhythm is originating from the sinus node. The PJCs will be interfused in the primary rhythm.
2. P WAVES: May occur before, during, or after the QRS depending on the location of the pacemaker in the junctional tissue.
3. PR INTERVAL: If the P wave occurs before the QRS complex, the PR interval will vary and will be shorter than normal (less than 0.12 second).
4. QRS: May be normal or aberrant.
5. CONDUCTION: The atria are stimulated in a retrograde fashion. The ventricular conduction is usually normal.
6. RHYTHM: Regular except for the premature junctional contraction.
7. COMMENTS: The patient may feel a skipped beat.
8. EXAMPLE:



C. Accelerated Junctional Rhythm and Paroxysmal Junctional Tachycardia

1. RATE: Accelerated junctional rhythm: 60 to 100.
   Paroxysmal junctional tachycardia: 100 to 250.
2. P WAVES: The position of the P wave in relation to the QRS will vary as to the rate of conduction in the junctional tissue. The configuration of the P wave will also vary accordingly. If the P wave is seen, it is usually inverted.
3. PR INTERVAL: If the P wave occurs before the QRS complex, the PR interval will be shorter than normal.
4. QRS: May be normal or aberrant.
5. CONDUCTION: Retrograde to the atria. Usually normal through the ventricles.
6. RHYTHM: Regular
7. COMMENTS: Must document on ECG to differentiate from sinus tachycardia and PAT. When a rapid junctional rhythm occurs with a bundle branch conduction defect, it is very difficult to differentiate this rhythm from ventricular tachycardia; therefore, it is very important to diagnose this rhythm rapidly.
8. EXAMPLE:

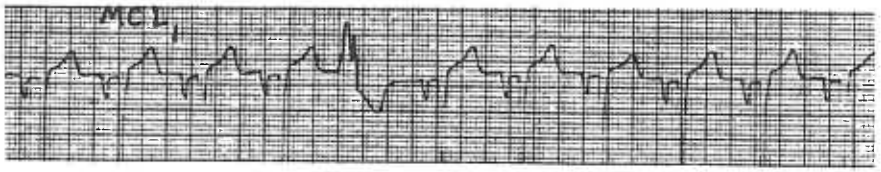


IV. Rhythms Originating in the Ventricle

A. Ventricular Premature Beats (PVCs)

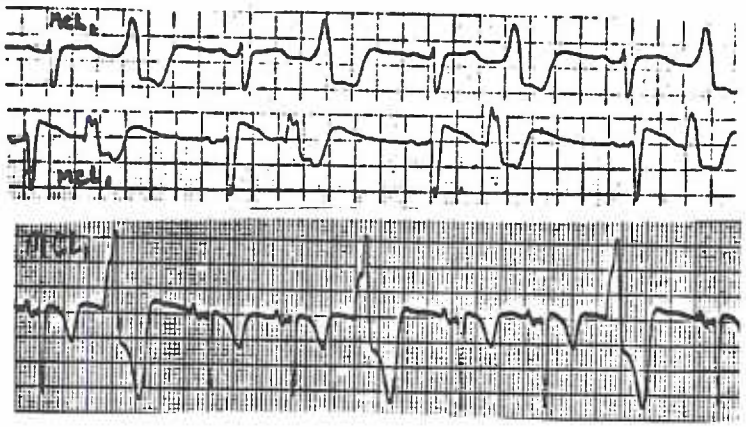
1. RATE: 60 to 100 if the rhythm is NSR.
2. P WAVES: May be completely obscured, hidden in the QRS of the premature beat. The sinus rhythm is usually uninterrupted, resulting in a complete compensatory pause. If a P wave is seen before the ventricular-looking QRS and if the P wave is premature, then the impulse is probably supraventricular with aberration and not a PVC.
3. PR INTERVAL: A PVC normally does not have a P wave preceding the QRS complex.
4. QRS: Usually wide and bizarre. Usually longer than 0.10 second. May have the same focus in the ventricle, or may have a wide variety of configurations if occurring from multiple foci in the ventricle.
5. CONDUCTION: There occasionally is retrograde conduction from the ventricle through the junctional tissue and atria.
6. RHYTHM: Irregular.
7. COMMENTS: Infrequent PVCs are not serious in themselves. Premature ventricular contractions may lead to more serious ventricular arrhythmias. Ventricular premature contractions are considered serious precursors of ventricular tachycardia and ventricular fibrillation when they have one of the following characteristics:
   (a) Occur in increasing number, more than 6 a minute
   (b) Are multifocal
   (c) Occur in pairs or triplets
   (d) Come on the T wave (R on T)

   PVCs are caused by hypoxia, fever, hypokalemia, myocardial ischemia, myocardial stretch, acidosis, alkalosis, and drug toxicity.
8. EXAMPLE:



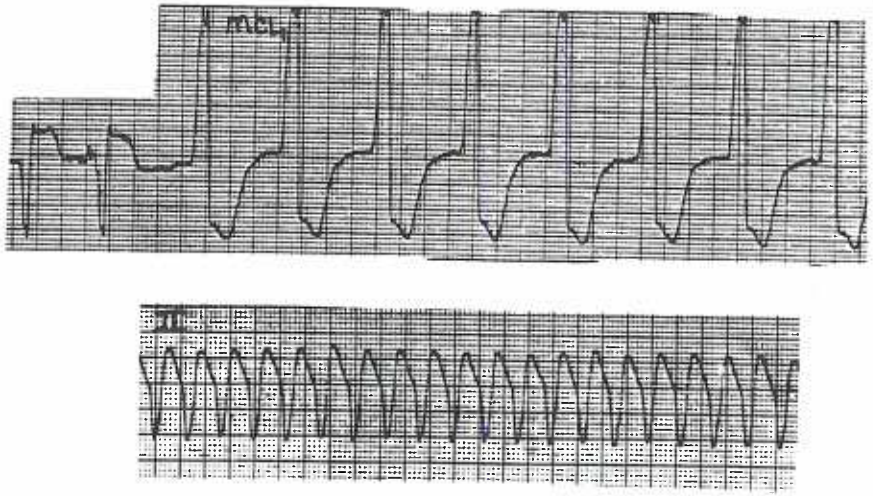
B. Ventricular Bigeminy

1. RATE: May occur at any heart rate; but rate is usually less than 90.
2. P WAVES: The same as described from PVCs; they may be hidden in the ventricular QRS.
3. PR INTERVAL: A P wave does not precede the QRS complex.
4. QRS: Every other beat is a PVC with a wide, bizarre QRS complex and a complete compensatory pause.
5. CONDUCTION: The sinus beats are conducted from the sinus node in a normal fashion. Alternating premature ventricular originate in the ventricles and may have retrograde conduction through the junctional tissue and atria.
6. RHYTHM: Regularly irregular
7. COMMENTS: Frequently associated with digitalis intoxication, acute myocardial infarction, and heart failure. The term bigeminy refers to the fact that every other beat is a premature beat. These premature beats may originate in the atria--atrial bigeminy, junctional tissue--junctional bigeminy, or ventricular tissue--ventricular bigeminy. If the premature beat occurs every third beat, it is termed trigeminy.
8. EXAMPLE:



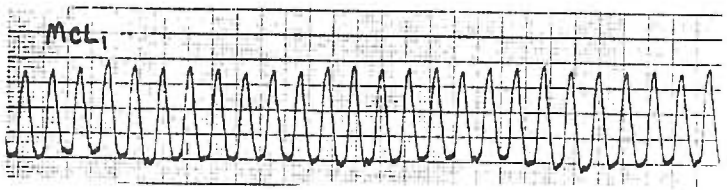
C. Idioventricular Rhythm, Accelerated Ventricular Rhythm, and Ventricular Tachycardia

1. RATE: Idioventricular rhythm 20-40 (escape rhythm), accelerated ventricular rhythm 40-100, and ventricular tachycardia 100-200.
2. P WAVES: Usually buried in the QRS; if seen, they would not necessarily fall in the normal pattern with the QRS.
3. PR INTERVAL: P waves usually do not precede the QRS complex.
4. QRS: Have the same configurations of a PVC, wide, bizarre, with T waves in the opposite direction. A ventricular beat may fuse with a normal QRS and is called a fusion beat. A normally conducted QRS may occur and is called a capture beat.
5. CONDUCTION: Originates in the ventricle with possible retrograde conduction to the junctional tissue and the atria.
6. RHYTHM: Usually is regular; but irregular ventricular tachycardias are also seen. The ventricular rhythm is rapid. The P waves, if seen, are slower and regular. There is no association between the sinus rhythm (P waves) and the ventricular rhythm (QRS complexes).
7. COMMENTS: Usually associated with heart disease; may precede ventricular fibrillation. This rhythm is extremely dangerous and should be considered an emergency. The patient is generally aware of this rapid rhythm and is quite anxious. The patient's tolerance or lack of tolerance to this rhythm will dictate the therapy to be taken.
8. EXAMPLE:



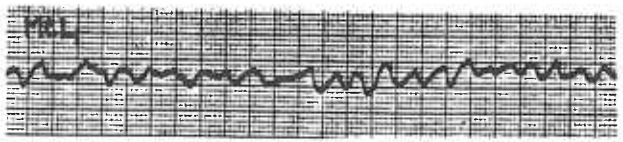
D. Ventricular Flutter

1. RATE: 200 to 400
2. P WAVES: No visible P waves are seen.
3. PR INTERVAL: None
4. QRS: Rapid, bizzare, picket-fence-type complexes. T waves are not visible.
5. CONDUCTION: Originates in ventricles. There may be retrograde conduction through the AV node and atria.
6. RHYTHM: Not precisely regular
7. COMMENTS: The clinical picture is exactly the same as ventricular standstill; the patient may be cyanotic and convulsing; there is no audible heart beat, no palpable pulse; the patient will not be breathing; diagnosis must be made by ECG. Usually fatal without immediate treatment.
8. EXAMPLE:



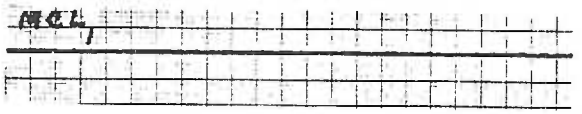
E. Ventricular Fibrillation

1. RATE: Rapid, uncoordinate, ineffective
2. P WAVES: Not seen
3. PR INTERVAL: None
4. QRS: Rapid, irregular, undulation without specific pattern (multifocal). The ventricles just have a quivering motion.
5. CONDUCTION: Foci are located in the ventricles, but so many foci are firing at one time that there is no organized conduction, i.e., no ventricular contractions occur, thus no cardiac output.
6. RHYTHM: Extremely irregular, uncoordinated, without specific pattern.
7. COMMENTS: Usually fatal without immediate treatment; only 5% convert spontaneously; no audible heart beat, no palpable pulse, no respirations; usually cyanotic and may be convulsing. This pattern is so grossly irregular, it can hardly be mistaken for another arrhythmia. Malfunction of the monitor may produce such a pattern, but in that case the clinical picture of the patient would rule out the diagnosis of ventricular fibrillation.
8. EXAMPLE:



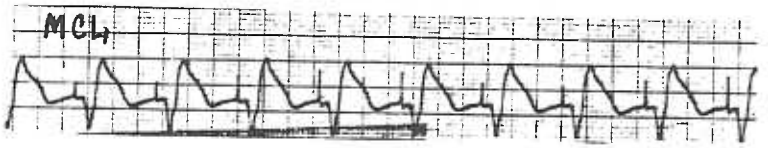
F. Ventricular Asystole

1. RATE: None
2. P WAVES: May see them, but they do not conduct through the AV node and ventricles.
3. PR INTERVAL: None
4. QRS: None
5. CONDUCTION: Possibly through the atria only.
6. RHYTHM: None
7. EXAMPLE:



G. Ventricular Pacemaker

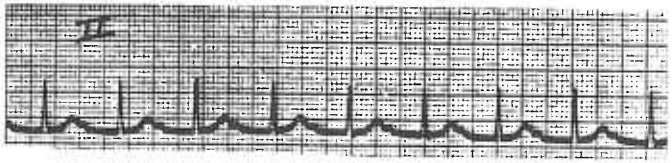
1. EXAMPLE:



V. AV Blocks

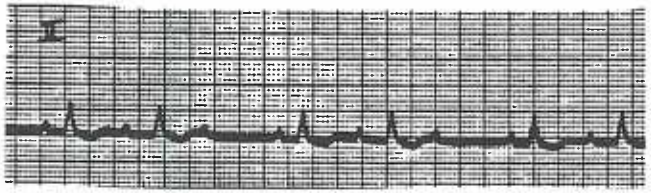
A. First Degree Heart Block

1. RATE: Variable. Usually 60 - 100.
2. P WAVES: Precede each QRS complex.
3. PR INTERVAL: The PR interval is greater than 0.20 second in duration.
4. QRS: Follows each P wave. Usually normal.
5. CONDUCTION: Delayed conduction anywhere between the atrial tissue and the Purkinje network produces a prolonged PR interval. Ventricular conduction is usually normal.
6. RHYTHM: Usually regular
7. COMMENTS: This arrhythmia is important since it may lead to more serious forms of heart block. It is often a warning signal. It is usually associated with organic heart disease. May be due to digitalis. A His Bundle recording may be done to pinpoint the area of block.
8. EXAMPLE:



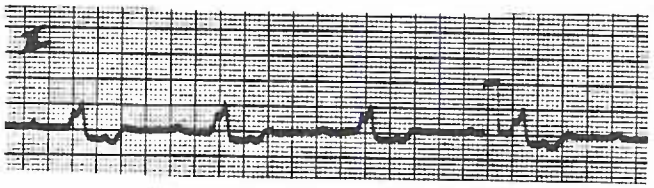
B. Second Degree Heart Block - Mobitz Type I - Wenckebach Phenomena

1. RATE: Variable. Usually 60 to 100.
2. P WAVES: Precede each QRS complex.
3. PR INTERVAL: The PR interval becomes increasingly longer until finally a QRS is dropped and then the cycle is repeated. Results in "group beating."
4. QRS: The R-R interval becomes progressively shorter until a QRS is dropped. QRS complex is usually of normal duration.
5. CONDUCTION: The PR interval becomes increasingly longer until an impulse is not conducted through the ventricles because it is blocked somewhere between the atrial tissue and the Purkinje network.
6. RHYTHM: Irregular
7. COMMENTS: Usually associated with organic heart disease; frequently due to digitalis intoxication. Seen frequently in patients with inferior myocardial infarction.
8. EXAMPLE:



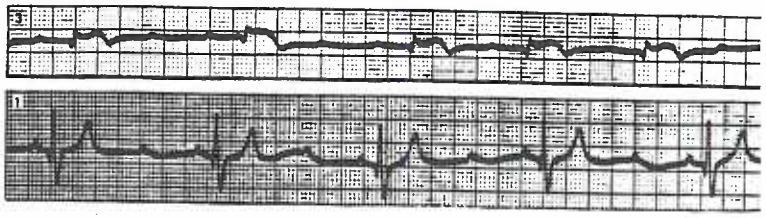
C. Second Degree Heart Block - Mobitz Type II

1. RATE: 30 to 55. The atrial rate may be two times faster than the ventricular rate.
2. P WAVES: There are occasionally or constantly two P waves for each QRS complex.
3. PR INTERVAL: The PR interval of the conducted beat is usually normal in duration.
4. QRS: Usually prolonged due to bundle branch block.
5. CONDUCTION: Atrial impulses are occasionally or alternately not conducted through the ventricles. Block occurs below the AV node.
6. RHYTHM: Usually slow and regular. When an irregularity is seen, it is due to the fact that the conduction is varying from 2:1 to 1:1 (normal).
7. COMMENTS: Frequently seen in patients with organic heart disease and digitalis intoxication; the slow heart rate reduces cardiac output. When second degree heart block occurs in a 2:1 pattern, it is not always clear whether it is type I or type II. Type I, 2:1 second heart block is characterized by prolonged PR intervals and normal QRS durations. Type II, 2:1 second degree heart block is characterized by normal PR intervals and wide QRS complexes.
8. EXAMPLE:



D. High-Grade (or advanced) Block

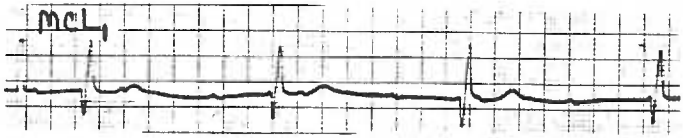
1. COMMENTS: High-grade block occurs when 2 or more atrial impulses (at a reasonable rate) fail to conduct to the ventricles. High-grade block represents a stage between 2:1 heart block and complete heart block. This block can be type I or type II as described above.
2. EXAMPLE:



E. Complete Heart Block - Third Degree Heart Block

1. ORIGIN: Impulses are originating in the sinus node, but these impulses are not being conducted through the AV node. They are completely blocked. Therefore, as an escape mechanism, the junctional area takes over as the pacemaker.
2. RATE: Atrial rate 60 to 100; ventricular rate 40 to 60.
3. P WAVES: The P waves originating from the sinus node will be seen regularly throughout the rhythm, but they will have no association with the QRS complexes. Since the rhythm conducting the QRS probably will have a supraventricular configuration but will not be preceded by a P wave.
4. PR INTERVAL: Variable
5. QRS: Normal supraventricular configuration; no association with the P waves. Occur regularly and slow.
6. CONDUCTION: Atrial impulses blocked completely at the AV node; junctional impulses conducted through the ventricle produce the QRS.
7. RHYTHM: Regular but slow
8. COMMENTS: Usually associated with organic heart disease; may be due to digitalis intoxication or myocardial infarction. Heart failure, shock, and cerebral anoxia may occur as a result of decreased rate.

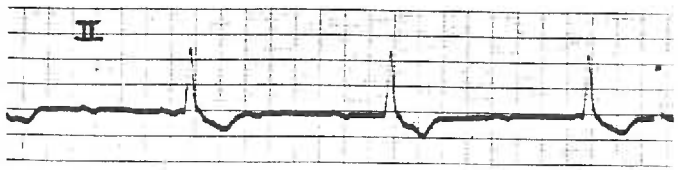
9. EXAMPLE:



F. Complete Heart Block - Third Degree

Pacemaker in the Ventricle

1. ORIGIN: Origin of impulses producing the QRS complexes is located in the ventricle; however, the sinus node usually is firing and P waves are seen throughout the rhythm; the P waves are blocked anywhere between the AV node and the Purkinje network.
2. RATE: Atrial rate 60 to 100. Ventricular rate 20 to 40.
3. P WAVES: Have no association with the QRS complexes.
4. PR INTERVAL: Variable
5. QRS: Arise from an impulse within the ventricles; the QRS interval is longer than 0.10; configuration is usually broad; slurred, appearing the same as a PVC.
6. CONDUCTION: The sinus node is firing and P waves can be seen. They are all blocked, and not conducted down to the ventricles.
7. RHYTHM: Usually slow but regular.
8. COMMENTS: Since the pacemaker in the ventricle is firing at such a slow rate, cardiac output is decreased, adequate blood pressure often is not maintained, cerebral perfusion is decreased and dizziness or fainting may occur; heart failure is imminent; electrical pacing is urgent in the presence of intolerance to the slow rhythm. The slow rhythm is not tolerated when the heart block occurred abruptly due to myocardial infarction.
9. EXAMPLE:



Examples of arrhythmias came from a variety of sources:

Carol Jacobson's private collection; Marriot and Connover "Advanced Concepts in Arrhythmias," C.V. Mosby, 1983, p. 278 (High-Grade Block); and California Heart Association "Introduction to Arrhythmia Recognition," 1968.

Appendix C

Summary by Year of Selected Studies on Periodicity of Heart Rate and Rhythm, Stroke Volume, and Cardiac Output

Abbreviations Used in Appendix C

AM	morning
ANOVA	analysis of variance
AR	atrial rate
AV	atrioventricular
B/P	blood pressure
BR	bedrest
CA	cancer
CCU	coronary care unit
CHB	complete heart block
CAU	caucasian
CHD	coronary heart disease
CI	cardiac index in liters per minute per meter squared
CO	cardiac output in liters per minute
CV	cardiovascular
CVD	cardiovascular disease
ECG	electrocardiogram
EEG	electroencephalogram
EOG	electroculogram
EPS	electrophysiology study
HR	heart rate in beats per minute
hr	hour(s)
ICU	intensive care unit
L:D	light to dark ratio
LV	left ventricular
min	minute
mo	months
MVP	mitral valve prolapse
MI	myocardial infarction
N	number
NL	normal
NS	nonsignificant
PACs	premature atrial contractions
PM	afternoon and evening
PSVT	paroxysmal supraventricular tachycardia
PVCs	premature ventricular contractions
R	rhythm
SA	sinoatrial
SCD	sudden cardiac death
SD	standard deviation
sec	second
SI	stroke index in ml per beat per meter squared
Subj	subject
SV	stroke volume in ml per beat
SVT	supraventricular tachycardia
URI	upper respiratory infection
VR	ventricular rate
VT	ventricular tachycardia
yr	year(s)

GUY (1839)
SUBJECTS: N=1, self; healthy. Age: adult. Gender: male
VARIABLE(S): HR
METHODS: FREQUENCY: 20 observations on first rising; 20 at night and a series of other observations
LENGTH: 8-9 AM to 12-2 AM
MEASUREMENT: sitting posture; state of rest; unexcited by food or exercise
TIME OF YEAR: spring, 1837
ANALYSIS: means and ranges only
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK: highest in morning
TROUGH: lowest at night
RANGE: 10
MEAN: AM:64, PM:54 and gradually diminished as the day advanced
SHAPE OF WAVEFORM:
OTHER: morning HR higher than evening and diminished in frequency more rapidly in the evening than in morning. The effect of food was greater and more lasting in the morning than evening.
LIMITATIONS: no data obtained during sleep. No cosinor analysis.

KLEITMAN, RAMSAROOP (1948)
SUBJECTS: N=10 Age: teenage to middleage Gender: N=6 males; N=4 females
VARIABLE(S): HR
METHODS: FREQUENCY: every 2 hr during the day and once or twice during sleep
LENGTH:
MEASUREMENT: self observation. 30 sec count of radial pulse. Sitting or lying after 15 min of rest. Measurements preceded meals.
TIME OF YEAR: October to March - Winter, May to August - Summer 1941-1945
ANALYSIS: data analyzed for each subject. Graphic. Fisher's T ($p<.01$)
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hours, weekly, monthly, seasonal
PEAK: early afternoon
TROUGH: during sleep (during day or night)
RANGE:
MEAN: 75 to 92, Jan - June, 1944 day active; 68 to 92, May - Oct, 1943.
SHAPE OF WAVEFORM: varied with individual
OTHER: HR increased after eating a meal. Curves in HR followed body temperature curves. $1^{o}F$ change resulted in 10-20 change in HR. Monthly (dicyclic) and seasonal rhythm in HR (N=3). HR increased in non-heating season.
LIMITATIONS: no cosinor analysis. Age of subjects unknown.

KLEITMAN, KLEITMAN (1953)
SUBJECTS: N=4, 4 members of a family lived above the Arctic Circle. Age: Parents middle aged; adult daughters
Gender: N=1 male, N=3 females
VARIABLE(S): HR
METHODS: FREQUENCY: N=2 HR counted every 3 hr on 18 hr day and every 4 hr on 28 hr day
LENGTH: 2 - three week periods
MEASUREMENT: In Norway (above Arctic Circle). 1 parent and 1 child had heart rates measured two 3-wk periods of: $1\text{-}18^{o}$ (6 hr sleep; 12 hr awake) with 2 meals; $2\text{-}28^{o}$ (8-9 hr sleep; 20-19 hr awake) with 3 meals
TIME OF YEAR: May 21 - July 23, 1951
ANALYSIS: graphs of individual data
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 18 hr and 28 hr
PEAK:
TROUGH: during sleep for both time periods
RANGE: 24 hr - 7.6 to 6.3; 18 hr - 12.3 to 25.8; 28 hr - 11.1 to 27.3
MEAN:
SHAPE OF WAVEFORM:
OTHER: prompt adjustment to non-24 hr period. The 18 hr day was more acceptable. Rest in bed decreased HR.
LIMITATIONS: small N. No cosinor analysis.

BROD AND VLADIMIR (1957)
SUBJECTS: N=27 (N=9 NLS; N=18 hypertensives) Age: not stated
Gender: not stated
VARIABLE(S): CO
METHODS: FREQUENCY: 4h
LENGTH: 2 consecutive days
MEASUREMENT: normal hospital ward; day active, out of bed. CO - impediance plethysmography (most CO checked with lobeline circulation time)
TIME OF YEAR: not stated
ANALYSIS: descriptive analysis; graphs
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24h
PEAK: day
TROUGH: night (all normals); in hypertensives, 7 out of 33 days CO either did not change or went up
RANGE: 6-7 L/min day to 4 L/min at night (even if subjects did not sleep during night)
MEAN: not provided
SHAPE OF WAVEFORM: sinusoidal
OTHER: SVR increases at night; BP did not change during night
LIMITATIONS: no cosinor analysis. Only 1 subject's graph of data presented

SNYDER, HOBSON, MORRISON, GOLDFRANK (1964)
SUBJECTS: N=12 healthy subjects Age: 18-26 yr Gender: N=5 males; N=7 females
VARIABLE(S): HR
METHODS: FREQUENCY: continuous and averaged at 5-min intervals
LENGTH: 2-6 nights of uninterrupted sleep in an experimental room
MEASUREMENT: photoelectric plethysmograph on a right toe, supplemented by ECG (lead I). EEG and eye movements were measured. Went to sleep between 0000 and 0100
TIME OF YEAR:
ANALYSIS: graphs of individual data. Mean and variability index. Hotelling T statistic and Scheffe's multiple comparisons.
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK:
TROUGH: during sleep onset, HR decreased 5-10%
RANGE:
MEAN:
SHAPE OF WAVEFORM:
OTHER: progressive decreases in heart rate with sleep. There was more variability during REM sleep that occurred later in the night.
LIMITATIONS: 24 hr data not collected

RICHARDSON, HONOUR, FENTON, STOTT, PICKERING (1964)
SUBJECTS: N=30 patients with increased B/P; N=8 patients without increased B/P Age: N=30 - 29-82 yr, N=8 - 13-51 yr. Gender: N=30, N=16 males; N=14 females
VARIABLE(S): HR
METHODS: FREQUENCY: 5 min intervals
LENGTH: 12 hrs (at least 4 hr sleep included)
MEASUREMENT: no antihypertensive drugs or sedatives. Sleep measured by EEG. Kept diaries. Slept 2300 to 0800. In hospital - encouraged to be out of bed during day.
TIME OF YEAR:
ANALYSIS: individual analysis. Graphic.
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK: with activity
TROUGH: during sleep
RANGE: 65-110
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER: reported HR data on only 2 subjects (1 without hypertension and 1 hypertensive)
LIMITATIONS: small N. Additional data not reported. No cosinor analysis. Measurements for only 12hr.

HAUTY, ADAMS (1966a)
SUBJECTS: N=4, healthy subjects Age: adult. Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: 30 sec intervals
LENGTH: Measurements for 1 week prior to jet flight to Manila, 8 days in Manila, and 1 week following return home (Oklahoma City) East-West flight.
MEASUREMENT: Left 1800 CST - transit time 23 1/2hr. Arrived 0730 (10hr time displacement). HR measured with cardiotachometer.
TIME OF YEAR:
ANALYSIS: Graphic
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: circadian
PEAK: 2100
TROUGH: 2400
RANGE: 84-95
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER: Phase shift in HR took 4 days for completion. When returning to home, phase shift took one day for completion.
LIMITATIONS: no cosinor analysis

HAUTY, ADAMS (1966b)
SUBJECTS: N=4, healthy subjects Age: adult. Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: 30 sec intervals
LENGTH: Measurements during the week prior to jet flight to Rome, 12 days in Rome, and during the 6 week following return to home (Oklahoma City)
MEASUREMENT: West-East flight. Left 1400 CST - transit time 15 1/2hr. Arrived 1230 (7hr time displacement). HR - cardiotachometer.
TIME OF YEAR:
ANALYSIS: Graphic
FINDINGS: PERIOD: Yes X, No ___, NA ___
LENGTH OF PERIOD: circadian
PEAK: 1800
TROUGH: 0700
RANGE:
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER: Phase shift in HR took 6-8 days for completion. When returning home, phase shift took one day to complete.
LIMITATIONS: no cosinor analysis

HAUTY, ADAMS (1966c)
SUBJECTS: N=4, healthy subjects Age: adult. Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: 30 sec intervals
LENGTH: 2 days in Washington DC, 12 days in Santiago, Chile, 1 week following return
MEASUREMENT: HR - cardiotachometer
TIME OF YEAR:
ANALYSIS: Graphic
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr
PEAK: 2400 (baseline)
TROUGH: 0700 (baseline)
RANGE: 69 to 76
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: no cosinor analysis

SCHAEFER, CLEGG, CAREY, DOUGHERTY, WEYBREW (1967)
SUBJECTS: N=2 healthy subjects Age: medical students. Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: HR continuously, averaged at 15 min intervals
LENGTH: 4 days control, 9 days isolation, 3 recovery
MEASUREMENT: constant environment, ECG - HR (telemetry), EEG - sleep
TIME OF YEAR: August
ANALYSIS: Graphic. Power spectrum analysis
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: Subject #1 - 25 ± 1.1hr; Subject #2 - 23.5 ± 1.7hr
PEAK: For 5 days of isolation, one after awakening and one later in day; the last 3 days of isolation only one peak in early hours after awakening.
TROUGH: during sleep (2nd part)
RANGE: Subject #1 = 43 ± 4.6 to 47 ± 11.8; Subject #2 = 52 ± 10.4 to 52 ± 3.8
MEAN: control period #1 - 62.5 ± 3.3; #2 - 70.5 ± 1.5; isolation period #1 - 61.1 ± 3.1; #2 - 68.5 ± 2.8
SHAPE OF WAVEFORM: 2 peaks and sinusoidal (24hr)
OTHER: sleep-wake period 25.75 ± 0.78
LIMITATIONS: no cosinor analysis

KHATRI & FREIS (1967)
SUBJECTS: N=15 NLs Age: 16-34 yr (22.3 yr) Gender: N=10 males; N=5 females
VARIABLE(S): HR, CO, & SV
METHODS: FREQUENCY: continuously. CO measured intermittently in the various stages of sleep
LENGTH: 2300 until the following morning
MEASUREMENT: day active. Slept in lab - sound proof. CO - dye dilution. CO obtained without going into room. N=9 also had CO measured using a Water's cuvette densimeter. EEG measured. Brachial artery cannulated.
TIME OF YEAR:
ANALYSIS: T-test
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK: while awake
TROUGH: sleep-all stages
RANGE:
MEAN: CO awake - 7.639 ± 1.248; CO asleep - 6.702 ± 1.27 (Stage I). HR awake - 66.2 ± 12.2; HR asleep - 62.6. SV awake - 117.6 ± 18.1; SV asleep - 108.1 (Stage I)
SHAPE OF WAVEFORM:
OTHER: CO decreased during sleep (due to decreased HR)
LIMITATIONS: no cosinor analysis

TATSUMI (1967)

SUBJECTS: N=44 with cardiac disease (N=27, dyspnea during day and night equal; N=10, advanced dyspnea; N=7, wheezing, LV failure) Age: N=7, 52-70 yr Gender: N=7, N=3 males; N=4 females

VARIABLE(S): HR, CI, SV/m^2

METHODS: FREQUENCY:
LENGTH:
MEASUREMENT: CO - precordial dilution method using I^{131} - Albumin. Day-1500, night-2200. Patients slept 1500-2000. Subjects were regrouped according to NYHA grades, Grade I N=3; Grade II N=24; Grade III N=10; Grade IV N=3.
TIME OF YEAR:
ANALYSIS: frequency only

FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK:
TROUGH:
RANGE:
MEAN:
SHAPE OF WAVEFORM:
OTHER:

HR

	N=27	N=10	N=7
Day (1500)	71 ± 6	82 ± 13	93 ± 17
Night (2200)	66 ± 5	73 ± 14	106 ± 17

CI

	N=27	N=10	N=7
Day (1500)	3.2 ± 0.4	3.0 ± 0.3	2.1 ± 0.7
Night (2200)	2.8 ± 0.3	2.6 ± 0.3	1.95 ± 0.5

SV/M^2

	N=27	N=10	N=7
Day (1500)	26 ± 24	57 ± 15	23 ± 5
Night (2200)	44 ± 16	50 ± 12	19 ± 5

HR

	I	II	III	IV
Day	70 ± 44	72 ± 14	86 ± 42	101 ± 19
Night	62 ± 9	67 ± 12	89 ± 55	118 ± 24

CI

	I	II	III	IV
Day	2.5 ± 0.2	3.4 ± 0.8	2.5 ± 0.2	2.4 ± 0.9
Night	2.1 ± 0.4	2.9 ± 0.7	2.2 ± 0.3	2.2 ± 0.6

SV/M^2

	I	II	III	IV
Day	37 ± 15	47 ± 18	29 ± 7	24 ± 6
Night	37 ±8	44 ± 13	27 ± 9	19 ± 4

LIMITATIONS: no cosinor analysis. Measurement only at 1500 and 2200.

KANEKO, ZECHMAN, SMITH (1968)

SUBJECTS: N=8 healthy subjects Age: 20-38 yr. Gender: males

VARIABLE(S): HR

METHODS: FREQUENCY: 5 times daily (0900 to 2230)
LENGTH: 1-3 days
MEASUREMENT: day active; ECG-HR
TIME OF YEAR:
ANALYSIS: Graphic. Cosinor

FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 25-27hr
ACROPHASE: 1600-1900
AMPLITUDE: 11
MESOR:
SHAPE OF WAVEFORM:
OTHER:

LIMITATIONS: no data during night. Incomplete reporting of cosinor analysis

BRISTOW, HONOUR, PICKERING, SLEIGHT (1969)
SUBJECTS: N=8 NLs; N=10 increased B/P; N=1 postural decreased B/P. Age: 23-58 yr; 35 ± 10.6 yr NLs; 47 ± 8.9 yr increased B/P. Gender: N=13 males; N=6 females
VARIABLE(S): CO, SV, HR, & R
METHODS: FREQUENCY: CO 3 times during the night; HR continuous and averaged every 5 min
LENGTH: 3 consecutive nights
MEASUREMENT: slept in laboratory. Lights were out at 2330 and subjects were awakened at about 0400-0500. None were receiving sedation or hypotensive therapy. All were in sinus rhythm. ECG-HR. EEG was obtained during sleep. CO was measured using dye-dilution method (in duplicate)
TIME OF YEAR:
ANALYSIS: means and SD only
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK:
TROUGH: HR decreased with sleep in all but 4 subjects
RANGE:
MEAN:
SHAPE OF WAVEFORM:
OTHER: Results are from the 3rd night. HR decreased 6.4 ± 6.4% for normals; 7.0 ± 5.1% for hypertensives. CO showed no consistent change in normals. In the hypertensives, CO fell 6.2% ± 13.6% during sleep (NS). CO before sleep were slightly higher than after sleep. Both groups had badycardia during sleep. One subject had frequent PACs. SV increased a mean of 11.2 ml during sleep in normals only.
LIMITATIONS: Data reported were measured on one night (2130-0530). No 24hr data collected. CO measured only 3 times in 8hr during night. No cosinor analysis.

ENGEL, HILDEBRANDT, VOIGT (1969)
SUBJECTS: N=10 healthy subjects Age: 18-32 yr Gender:
VARIABLE(S): HR
METHODS: FREQUENCY: 1 hr intervals
LENGTH: 2-24 hr periods
MEASUREMENT: ECG-HR. Confined to bed.
TIME OF YEAR:
ANALYSIS: Graphic.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
PEAK: 1800
TROUGH: 0430
RANGE: 60-69 = 9 - (13.2%)
MEAN: 64.5
SHAPE OF WAVEFORM: cosine
OTHER:
LIMITATIONS: no cosinor analysis

ASCHOFF, ASCHOFF (1969)
SUBJECTS: N=8 Age: 18-19 yr Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: 3 hr intervals
LENGTH: 24 hr
MEASUREMENT: ECG-HR. Sleep period 2200-0600. Subj 1:0900 to 0900; subj 2:1200 to 1200; subj 3:1500 to 1500; subj 4:1800-1800; subj 5:2100-2100; subj 6:2400-2400; subj 7:0300 to 0300; subj 8:0600-0600.
TIME OF YEAR:
ANALYSIS: Graphic.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD:
PEAK: 2100
TROUGH: 0300
RANGE: 45-70=25
MEAN:
SHAPE OF WAVEFORM:
OTHER:
LIMITATIONS: study was designed to measure HR & BP responses to 10 min tilt, so baseline measures at each 3 hr interval were preparatory to a tilting procedure.

REINBERG et al. (1970)
SUBJECTS: N=7, healthy subjects Age: 18-45 yr. Gender: N=3 females; N=4 males
VARIABLE(S): HR
METHODS: FREQUENCY: 4 hr intervals
LENGTH: 24 hr
MEASUREMENT: Two regimens: 1. habitual activity and diet; 2. 36-hr bedrest, meals every 4 hr. Darkness 2300-0800
TIME OF YEAR: March through September
ANALYSIS: Cosinor. Reference to sleep made
FINDINGS: PERIOD: Yes _X_, No ___ ($p<.005$)
LENGTH OF PERIOD: 24 hr
ACROPHASE: 1 = 1300 (1048, 1440)
2 = 1030 (0736, 1328)
AMPLITUDE: 1=7.7 (4.5 to 10.9); 2 = 4.8 (2.6 to 6.9)
MESOR: 1 = 75.2 ± 3.2
2 = 68.7 ± 3.1
SHAPE OF WAVEFORM: sinusoidal
OTHER: rhythm not directly dependent on cycles of rest activity
LIMITATIONS: none noted

F. HALBERG, et al. (1970)
SUBJECTS: N=5, healthy subjects Age: 35-38 yr. Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: 1-15 hr
LENGTH: 5-11 days
MEASUREMENT: ECG - HR - tape recorded astronauts in flight
TIME OF YEAR:
ANALYSIS: Cosinor: single, group. Reference to sleep made: midsleep
FINDINGS: PERIOD: Yes _X_, No ___ ($p<.02$)
LENGTH OF PERIOD: 24hr
ACROPHASE: 1116 to 1756
AMPLITUDE: 11-14 ± 2-7
MESOR: 54-77 ± 1.1-4.5
SHAPE OF WAVEFORM: sinusoidal
OTHER: N=6 BR (no exercise) for 4 days - 4 hr intervals - Mesor = 63 ± 3, Amplitude = 5 (3,7), Acrophase = 1324; N=6 BR (with exercise) for 4 days - 4 hr intervals - Mesor = 69 ± 4, Amplitude = 9 (2,11), Acrophase = 1256; N=7 Astronauts in flight 3-11 days - 1-10 hr intervals - Mesor = 68 ± 3, Amplitude = 8 (3,14), Acrophase = 1300
LIMITATIONS: none noted

SOBOTKA, MAYER, BAUERNFEIND, KANAKIS, ROSEN (1971)
SUBJECTS: N=50, healthy subjects Age: 22-28 yr. Gender: females
VARIABLE(S): HR & R
METHODS: FREQUENCY: continuous
LENGTH: 24h
MEASUREMENT: ECG - HR & R (Avionics). Followed normal daily routines and kept diaries.
TIME OF YEAR:
ANALYSIS: scanner used. T-test, Chi square test
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK: during awake period
TROUGH: during sleep period
RANGE: during waking HR - 56 ± 7 to 153 ± 14 (90 ± 11); during sleep HR - 48 ± 6 to 105 ± 13 (66 ± 9)
MEAN: HR - 82 ± 9 (60-103)
SHAPE OF WAVEFORM:
OTHER: N=32 had PACs; N=27 had PVCs (N=4 increased with sleep; N=21 increased while awake; N=2 same awake or asleep); N=1 had VT; N=2 Type I 2^{o} AV block. All had sinus bradycardia and sinus arrhythmia sometime during sleep.
LIMITATIONS: no cosinor analysis

WINGET, VERNIKOS-DANELLIS, CRONIN, LEACH, RAMBAUT, MACK (1972)
SUBJECTS: N=8, healthy subjects Age: Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: 4 hr interval
LENGTH: 6 day pre BR, 56 days BR, 10 day recovery
MEASUREMENT: defined environment 0900 lights on. 14L:10D. 2300 lights off. Subjects were hand fed. ECG - HR
TIME OF YEAR:
ANALYSIS: Graphic. Summation dial
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: circadian
PEAK: bedrest 1930 - recovery 2330
TROUGH: bedrest 0330 - recovery 0330-1130
RANGE: 14 beats
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: no cosinor analysis. Age unknown. 4 hr interval may not be frequent enough to detect daily changes.

SMITH, JOHNSON, ROTHFELD, ZIR, THARP (1972)
SUBJECTS: N=18 patients in CCU, with arrhythmias.
Age: 41-73 yr (57yr). Gender:
VARIABLE(S): PVCs and PACs
METHODS: FREQUENCY: continuous
LENGTH: 6 1/2 hr of sleep
MEASUREMENT: evening of admission, EEG, EOG, ECG
TIME OF YEAR:
ANALYSIS: scored by visual inspection. T-tests, rank order trend test
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK:
TROUGH:
RANGE:
MEAN:
SHAPE OF WAVEFORM:
OTHER: N=17 had PVCs. Increased PVCs during wake-sleep transition; N=6 had increased PVCs while awake; N=6 had increased PVCs during REM; N=5 had increased PVCs during non-REM; N=11 (of N=17) had two or more PVCs in a row (NS between awake and sleep); N=7 (of N=10) had two or more PACs in a row (NS between awake and sleep); N=10 had PACs; N=4 had increased PACs while awake; N=3 had increased PACs during REM; N=2 had increased PACs during non-REM; N=1 had increased PACs during wake and non-REM
LIMITATIONS: no cosinor analysis. Gender unknown

KELLEROVA, KITTOVA (1973)
SUBJECTS: N=11, healthy subjects Age: 21-25 yr. Gender:
VARIABLE(S): HR
METHODS: FREQUENCY: 3 hr intervals
LENGTH: 0900-2100
MEASUREMENT: ECG-HR, no marked physical or mental strain
TIME OF YEAR:
ANALYSIS: Graphic.
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK: 1500
TROUGH: 2100
RANGE: 63-67
MEAN:
SHAPE OF WAVEFORM:
OTHER:
LIMITATIONS: no data during sleep. No cosinor analysis. Gender unknown

KUZEL (1973)
SUBJECTS: N=6, patients with MI, 2 to 62 hr post admission. (1 patient's MI was ruled out)(N=4 black; N=2 caucasian)
Age: 55-78 yr Gender: males
VARIABLE(S): HR & R
METHODS: FREQUENCY: continuous and averaged at 1 hr interval
LENGTH: 24 hr
MEASUREMENT: In CCU. ECG-HR & R fed directly into computer. Day began at 0630.
TIME OF YEAR: Mar 22, 1971-Sept 29, 1971
ANALYSIS: Cosinor: individual and group. HR & arrhythmia analyzed by computer.
FINDINGS: PERIOD: Yes X, No ___ HR
LENGTH OF PERIOD: 24 hr for N=6; 16 hr for N=4; 4.8 hr for N=2; 8 hr for N=2; 2.82 hr and 1.41 hr for N=1.
ACROPHASE: 0100 (0012, 0216) to 1525 (1348, 1701)
AMPLITUDE: 4.9 ± 1.1 - 8.1 ± 1.1
MESOR: $63.8 \pm .8$ - $96.6 \pm .1$
SHAPE OF WAVEFORM: sinusoidal
OTHER: PACs - Group acrophase 0902 (0728, 1845). Significant 12 hr for N=4; 3.4 hr for N=1; 0.06-1.6 hr for N=5. PVCs - 24 hr for N=3 (acrophases 0743 to 1820); 12 hr for N=1; 8 hr for N=2; 4.8 hr for N=2; 5.3 hr for N=1; 4 hr for N=1; .6 - 1.5 for N=2. Junctional escape beats - 24 hr for N=4 (acrophases 0550 to 1621). 16 hr for N=1; 12 hr for N=3; 8 hr for N=2; 3.4 hr for N=1; .5 - 2.7 for N=2.
LIMITATIONS: conflicting data in tables. Unknown if subjects had been day active prior to admission.

MALMSTROM (1973)
SUBJECTS: N=1 Cauc, NLs Age: 37 yr Gender: male
VARIABLE(S): HR
METHODS: FREQUENCY: once daily (1126 ± 20)
LENGTH: 1 yr
MEASUREMENT: employed during day Mon --> Fri sedentary job. Pulse was self counted x 2 and averaged. Readings were 30 minutes before lunch and 3.5 hr after breakfast.
TIME OF YEAR: in San Francisco July 14, 1969 to July 13, 1970.
ANALYSIS: Chi square. Graphic
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: circaseptan (weekly)
PEAK: Saturday and Monday (p<.01)
TROUGH: Sunday p<.001
RANGE: 52-84
MEAN: 65.9
SHAPE OF WAVEFORM: 2 peaks.
OTHER: sociocultural stimuli influenced rhythm. Tues through Fri were similar.
LIMITATIONS: no cosinor analysis

KANABROCKI, SCHEVING, HALBERG, F, BREWER, BIRD (1973)
SUBJECTS: N=13; 1 yr later another N=12, healthy subjects Age: 23-29 yr (26 yr) Gender: male
VARIABLE(S): HR
METHODS: FREQUENCY: 3 hr interval
LENGTH: 30 hr
MEASUREMENT: radial pulse counted. Rest: 2245-0700 on cots in darkened room. Activity: 0700-2245. Ate meals at 0830, 1430, 1630. The group was asked to abstain from any unusual or strenuous activity from 0700 to 1245. In the 1971 series, Rest: 2100-0600. Meals: 0700, 1245, and 1645.
TIME OF YEAR: May 14, 1969 and in 1971
ANALYSIS: Cosinor: single and group
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: circadian 1969 and 1971 (p<.001 Group); (p<.05 in N=6 in 1969); (p<.05 in N=8 in 1971)
ACROPHASE: 1969: 1240 (1228, 1352); 1971: 1420 (1308, 1520)
AMPLITUDE: 1969: 7.47 ± 2.82; 1971: 6.39 ± 3.03
MESOR: 1969: 63 ± 2; 1971: 73.7 ± 2.4
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: none noted

GERVAIS, et al (1973)
SUBJECTS: N=27 (N=20 in toxic coma, grade II-IV from suicide attempt - overdose; N=7 controls) Age: N=20 - 19-81 yr; N=7 - 18-45 yr (36.2 to 37.4). Gender: N=20, N=5 males, N= 15 females; N=7, N=4 males, N=3 females
VARIABLE(S): HR
METHODS: FREQUENCY: 4 hr
LENGTH: 24 hr
MEASUREMENT: radial pulse counted
TIME OF YEAR: coma subjects - January-July; controls - unknown
ANALYSIS: Cosinor
FINDINGS: PERIOD: Yes X, No ___ p<.002 for controls only
LENGTH OF PERIOD: 24 hr
ACROPHASE: 1356 (1104, 1656)
AMPLITUDE: 7.7 (4.5, 10.9)
MESOR: 75.2 ± 3.2; for patients 97.2 ± 3.5
SHAPE OF WAVEFORM: sinusoidal (control)
OTHER:
LIMITATIONS: patients were not homogeneous (3 were greater than 70 years old, some received sympathomimetics) and data were grouped. No individual analysis prior to grouping.

REINBERG, GERVAIS, POLLAK, ABULKER, DUPONT (1973)
SUBJECTS: N=27 (N=7, healthy subjects; N=20 patients in deep coma [II-IV] following overdose of drugs) Age: NLs 18-45 yr; patients 19-71 yr (37 yr) Gender: Patients - N=5 males; N=15 females; NLs - N=4 males; N=3 females.
VARIABLE(S): HR
METHODS: FREQUENCY: 4 hr intervals (0300, 0700, 1100, 1500, 1900, 2300)
LENGTH: 24 hr
MEASUREMENT: prior to study all had diurnal activity (0800-2300); slept 2300-0800. Radial artery pulse counted for one min.
TIME OF YEAR: Jan-July, 1972
ANALYSIS: Cosinor: group (24 hr & 24.7 hr).
FINDINGS: PERIOD: Yes X, No ___ p<.005 in NLs only.
LENGTH OF PERIOD: 24 hr
ACROPHASE: 1356 (1104, 1656)
AMPLITUDE: NLs: 7.7 (4.5, 10.9)
MESOR: NLs: 75.2 ± 3.2; Patients: 97.2 ± 3.5
SHAPE OF WAVEFORM:
OTHER: those in coma showed alteration in HR circadian rhythm.
LIMITATIONS: no individual cosinor analysis of those in coma. 4 hr interval may be too long an interval to detect change in these ill adults.

LOWN, TYKOCINSKI, GARFEIN, BROOKS (1973)
SUBJECTS: N=54 (N=31 with CHD; N=11 with misc HD; N=12 NL)
Age: CHD 55 yr (33-76); Misc 54.2 yr (33-68); NL 48 yr (26-28)
Gender: CHD - N= 28 males, N=3 females; Misc HD; N=6 males, N=5 females; NLs - N=8 males, N=4 females
VARIABLE(S): PVCs, HR
METHODS: FREQUENCY: continuous
LENGTH: 24hr
MEASUREMENT: ECG - HR - taped. Regular routines followed. Slept at home. Kept diary.
TIME OF YEAR:
ANALYSIS: frequency only
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK: while awake - HR
TROUGH: during sleep - HR
RANGE:
MEAN:
SHAPE OF WAVEFORM:
OTHER: 83.3% had PVCs; N=22 (patients) decreased frequency of PVCs by 50% during sleep; N=13 (patients) decreased frequency of PVCs by 25-50% during sleep; when those without PVCs were excluded, 78% had slowed frequency of PVCs during sleep; PVC grade was lower during sleep (Grade 0-5) (2.75 grade --> 1.78 while asleep) $p<.001$; HR decreased with sleep - lowest during late sleep period.
LIMITATIONS: No hourly description of HR and PVCs. No cosinor analysis.

HOCKENBERGER, RUBIN (1974)
SUBJECTS: N=10, MI patients in CCU with PVCs and no lidocaine
Age: Gender: males
VARIABLE(S): PVCs
METHODS: FREQUENCY: continuous. 6 hr interval averages
LENGTH: 4 days post MI
MEASUREMENT: ECG - R
TIME OF YEAR:
ANALYSIS: used computer to interpret arrhythmias. Average over 6 hrs
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK:
TROUGH:
RANGE:
MEAN:
SHAPE OF WAVEFORM:
OTHER: PVC/min: day-1 2.0-2.5 - 1200 to 2400; day-2 3.5 - 1200 to 1800; day-3 2.5 - 0600 to 1200; day-4 1.0 all day
LIMITATIONS: reliability of arrhythmia coding was presumed. Used computerized print out which probably included artifact. Age unknown. No cosinor analysis.

RUMMEL (1974)
SUBJECTS: N=3 Astronaut, Apollo 15 mission Age: Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: 30 min
LENGTH: 8 days +
MEASUREMENT: ECG - HR
TIME OF YEAR: July 26, 1971
ANALYSIS: spectral analysis. Multiple time series regression analysis.
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 21.5-24 hr, 90 min (60, 160)
PEAK:
TROUGH:
RANGE: 6.0 ± 2.4 to 9.6 ± 3.5
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: no cosinor analysis

ORR, HOFFMAN (1974)
SUBJECTS: N=12, healthy subjects Age: 18-27 yr Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: continuous. Averaged for 10 min intervals
LENGTH: 23 hr
MEASUREMENT: start 0900 --> 0800. ECG - HR in laboratory. Reclined in bed. Void X 2 (mid AM and late evening)
TIME OF YEAR:
ANALYSIS: periodogram analysis, complex demodulation
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 87-94 mins
ACROPHASE:
AMPLITUDE:
MESOR:
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: no cosinor analysis

WERTHEIMER, HASSEN, DELMAN, YASEEN (1974)
SUBJECTS: N=10 patients without CV disease Age: 18-48 yrs (28.5 yr) Gender:
VARIABLE(S): HR
METHODS: FREQUENCY: HR measured continuously - averaged every 2 hr
LENGTH: 24 hr
MEASUREMENT: ECG - HR; BR, supine, no medications or smoking; BR - 24 hr prior to study; hospital routine followed
TIME OF YEAR:
ANALYSIS: Graphic. Student t-test between minima and maxima
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr
PEAK: 6 PM
TROUGH: 6 AM
RANGE: 77.4 ± 3.7 to 71.4 ± 3.2
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER: 6 AM to 9 PM - HR increased; 9 PM to 6 AM - HR decreased
LIMITATIONS: gender unknown. No cosinor analysis.

HALBERG, BUCHWALD, CHARYULU, REEKER (1974)
SUBJECTS: N=1 with breast CA Age: 44 yr at start
Gender: female
VARIABLE(S): HR
METHODS: FREQUENCY: unknown
LENGTH: 1967-1969
MEASUREMENT: self measurement
TIME OF YEAR: Sept 1967 - Nov 1967; Oct 28, 1968 - May 18, 1969
ANALYSIS: Cosinor
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr
ACROPHASE: 1968: 1212 (1052, 1332); 1967: 0900 (0640, 1124)
AMPLITUDE: 1968: 5.2 ± 0.7; 1967: 3.4 ± 0.7
MESOR: 1968: 75 ± 0.58; 1967: 73 ± .54
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: only one subject. Frequency of HR measurement unknown.

WINGET, VERNIKOS-DANELLIS, LEACH, RAMBAUT (1974)
SUBJECTS: N=8, healthy subjects Age: Gender: male
VARIABLE(S): HR
METHODS: FREQUENCY: 6 times daily; 2330, 0330, 0730, 1130, 1530, 1930
LENGTH: 82 days
MEASUREMENT: lights on 0900; 16L:8D - 6 days prebedrest, 56 days bedrest, 10 days recovery. ECG-HR, 2 subjects per room
TIME OF YEAR:
ANALYSIS: Graphic. Summation dial
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr
PEAK: during BR - 1930; after BR - 2330
TROUGH: during BR - 0330; after BR - 1130
RANGE: during: 63-76; after: 75-98
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER: mean HR increased during BR
LIMITATIONS: no cosinor analysis. Age unknown

ORR, HOFFMAN, HEGGE (1974)
SUBJECTS: N=11, healthy subjects Age: young (college students) Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: continuous, averaged at 10 min intervals
LENGTH: 21-44 hr
MEASUREMENT: ECG - HR
TIME OF YEAR:
ANALYSIS: complex demodulation
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 90 ± 5 min
PEAK:
TROUGH:
RANGE:
MEAN:
SHAPE OF WAVEFORM:
OTHER:
LIMITATIONS: no cosinor analysis

F. HALBERG, et al. (1974)
SUBJECTS: N=50 students Age: 13-18 yr Gender:
VARIABLE(S): HR
METHODS: FREQUENCY: continuous
LENGTH: 16-64 days
MEASUREMENT: ECG - HR (taped)
TIME OF YEAR:
ANALYSIS: Cosinor. Reference to sleep: midsleep
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
ACROPHASE: 1308 (1148, 1440)
AMPLITUDE:
MESOR:
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: gender of subjects not known. Incomplete reporting of data from cosinor analysis.

FREEDMAN, RAMCHARAN, HOAG, GOLDFIEN (1974)
SUBJECTS: N=8786 Age: 18-50 yr (35.4 yr non-users; 30.2 yr users of oral contraceptives) Gender: females
VARIABLE(S): HR
METHODS: FREQUENCY: daily
LENGTH: 3 yr
MEASUREMENT: ECG - HR. Data collected daily between 0800-1400.
TIME OF YEAR: Dec 1968 - Feb 1972
ANALYSIS: Graphic. Cosinor.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 28-30 days
ACROPHASE:
AMPLITUDE: 1-2
MESOR:
SHAPE OF WAVEFORM: sinusoidal
OTHER: slight increase in HR over menstrual cycle in both groups. Large between subject variation.
LIMITATIONS: data from cosinor analysis not provided

WINGET, VERNIKOS-DANELLIS, DEROSHIA, CRONIN, LEACH, RAMBAUT (1974)
SUBJECTS: N=12, healthy subjects Age: 20-26 yr Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: 2 hr interval
LENGTH: 96 days
MEASUREMENT: N=6 - 56 days of complete bed rest followed by 20 days recovery. N=6 control (ambulatory) constant environment 20 days. 14L:10D lights on at 0900. TV allowed. Hand fed - 0900, 1300, 1730, 2200. ECG - HR.
TIME OF YEAR:
ANALYSIS: periodogram, correlogram, and summation dial
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: circadian in both groups
PEAK: 1600 (control)
TROUGH: during sleep
RANGE: lower for those on bedrest
MEAN: 70s BR and 80s Ambulatory
SHAPE OF WAVEFORM: sinusoidal
OTHER: bedrest decreased the amplitude of the rhythm. Rhythm asynchrony between HR and temperature after 20 days of bedrest.
LIMITATIONS: no cosinor analysis

ENNA, SCHEVING, F. HALBERG, JACOBSON, MATHER (1974)
SUBJECTS: N=10 patients with leprosy Age: 29-66 yr
Gender:
VARIABLE(S): HR
METHODS: FREQUENCY: 3 hr intervals from 0600-2100
LENGTH: 10 days
MEASUREMENT: radial pulse counted
TIME OF YEAR:
ANALYSIS: Graphic: chronograms. Cosinor: single and group. Midsleep (2130-0600)
FINDINGS: PERIOD: Yes X, No ___ p <.05
LENGTH OF PERIOD: 24 hr
ACROPHASE: 1540 (1956, 2024)
AMPLITUDE: 4.78 ± 4.76
MESOR: 78 ± 3
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: no data obtained during sleep. Gender unknown.

POBLETE, KENNEDY, CARALIS (1974)
SUBJECTS: N=90 patients with stable CHD and N=30 NLs
Age: N=90, 57 ± 8 yr; N=30 47 ± 9 yr Gender:
VARIABLE(S): PVCs
METHODS: FREQUENCY: continuous
LENGTH: 24 hr
MEASUREMENT: ECG - Holter. 10 patients were on medications. All engaged in usual daily outpatient activities. 3 were ambulatory in hospital. Diaries kept.
TIME OF YEAR:
ANALYSIS: scanner used. Graphic
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK:
TROUGH:
RANGE:
MEAN:
SHAPE OF WAVEFORM:
OTHER: 86% of patients had PVCs (N=77); 40% of NLs had PVCs (N=12); 60% of patients had multiformed PVCs and repetitive patterns of PVCs; 13% of NLs had multiformed PVCs and repetitive patterns of PVCs. VT - 7% of patients. Couplets - 13% of patients. Multiformed 29% of patients.
LIMITATIONS: no cosinor analysis. Gender unknown

SMOLENSKY, KRAFT, SOTHERN, DOWNS, EIFLER, MEALY (1975)
SUBJECTS: N=3 heart transplant patients Age: 6th - 7th decade Gender:
VARIABLE(S): HR
METHODS: FREQUENCY: 15 min intervals from continuous data
LENGTH: 1 or more 72 hr spans
MEASUREMENT: active 0700-2230; rest 2230-0700. ECG-HR.
TIME OF YEAR:
ANALYSIS: Cosinor: single & group (24 hr, 12 hr, 8 hr, & 6 hr used)
FINDINGS: PERIOD: Yes X, No ___ p<.05 Donor HR
LENGTH OF PERIOD: 24 hr
ACROPHASE: 1656 (0940, 2100)
AMPLITUDE: 7.7 (.1, 15.4)
MESOR: 90 ± 12.8
MEAN:
SHAPE OF WAVEFORM:
OTHER:
LIMITATIONS: small N

CHRIST, HOFF (1975)
SUBJECTS: N=1 with CHB in good health Age: 19 yr
Gender: female
VARIABLE(S): HR
METHODS: FREQUENCY: continuous. Averaged into 30 min intervals.
LENGTH: 63 hr
MEASUREMENT: complete BR with BRP, Lead II, ECG - HR
TIME OF YEAR: March, 1969
ANALYSIS: Graphic. Cross covariance
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
PEAK: during day (AM shortly after awakening)
TROUGH: during night (AM shortly before awakening)
RANGE: atrial rate - 58-80; ventricular rate - 33-47
MEAN: 67 (AR); 40 (VR)
SHAPE OF WAVEFORM:
OTHER:
LIMITATIONS: no cosinor analysis

WINKLE, LOPES, FITZGERALD, GOODMAN, SCHROEDER, HARRISON (1975)
SUBJECTS: N=24 patients with MVP Age: 23-70 yr, (45.9 yr)
Gender: N=5 males; N=19 females
VARIABLE(S): HR and R
METHODS: FREQUENCY: continuous
LENGTH: 24 hr
MEASUREMENT: ambulatory ECG (Avionics), no antiarrhythmics. Kept diaries.
TIME OF YEAR:
ANALYSIS: ECG analyzed for 15 min periods - 96 in 24 hrs. Frequency only.
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK: HR increased while awake
TROUGH: HR decreased with sleep
RANGE:
MEAN: while awake - 67 ± 9 to 121 ± 14; while asleep - 56 ± 8 to 95 ± 12
SHAPE OF WAVEFORM:
OTHER: N=18 had ventricular arrhythmias; decreased PVCs with sleep. N=15 had atrial arrhythmias; decreased PACs with sleep. N=9 had both types.
LIMITATIONS: did not examine time of day and incidence of arrhythmias or HR

LOWN, CALVERT, ARMINGTON, RYAN (1975)
SUBJECTS: N=184, patients with CHF (N=100 outpatients; N=84 inpatients) Age: outpatients - 57 yr Gender: males
VARIABLE(S): PVCs
METHODS: FREQUENCY: continuous
LENGTH: 24 hr
MEASUREMENT: ECG - HR taped
TIME OF YEAR:
ANALYSIS: Frequency
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK:
TROUGH:
RANGE:
MEAN:
SHAPE OF WAVEFORM:
OTHER: 88% had ventricular ectopy; 27% had ventricular couplets; 14% had 3 or more PVCs in a row. Daily variation in occurrence of ventricular ectopies seen.
LIMITATIONS: no cosinor analysis

KENNEDY, UNDERHILL (1976)
SUBJECTS: N=25 asymptomatic health subjects with frequent (>3/min) or complex PVCs Age: 4th to 7th decade Gender:
VARIABLE(S): HR and R
METHODS: FREQUENCY: continuous
LENGTH: 24 hr
MEASUREMENT: ECG - HR (Holter-Avionics). Usual hours of sleep/wake cycle. Diary kept.
TIME OF YEAR: during 18 months
ANALYSIS: frequency awake and asleep only
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK: 74% had increased PVCs with activity during day
TROUGH: at night with sleep
RANGE:
MEAN:
SHAPE OF WAVEFORM:
OTHER: complex PVCs in all; decreased PVC couplets with sleep; 26% increased multifocal PVCs with sleep.
LIMITATIONS: no cosinor analysis. Gender unknown.

CLARK, HAMER, SHELTON, TAYLOR, VENNING (1976)
SUBJECTS: N=86 NLs Age: 16-65 yr
Gender: N=41 males; N=45 females
VARIABLE(S): HR and R
METHODS: FREQUENCY: continuous
LENGTH: 2-24 hr periods
MEASUREMENT: ECG - Avionics. HR taped. Diary kept
TIME OF YEAR:
ANALYSIS: computer was used to detect arrhythmias. Graphic analysis
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr - HR
PEAK: females - 0800; males - 1300 and 0830
TROUGH: females - 0400-0530; males 0530
RANGE: females 66-95; males 59-85
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER: N=1- (12%) had serious arrhythmias. Most had SVT, PVCs, junctional rhythm, and 2° AV heart block. Bradyarrhythmias and tachyarrhythmias were equally common in waking and sleeping hours. PVCs seen in 63 subjects (male=31; female=32).
LIMITATIONS: time of day of arrhythmias was not presented. No cosinor analysis.

BAUST, IRMSCHER, JORG, SOMMER (1976)
SUBJECTS: N=6 patients with epilepsy (awakening type); N=3 control patients (increased BP, renal failure, stroke)
Age: epileptics: 10-35 yr; controls 24-61 yr
Gender: epileptics - N=5 males; N=1 female. Control - N=3 males.
VARIABLE(S): HR
METHODS: FREQUENCY: 1 hr interval
LENGTH: 72 hr
MEASUREMENT: constant environmental conditions in hospital. No medications. Sleep period 2200 to 0600. HR daytime by palpation; HR during sleep by ECG.
TIME OF YEAR: Jan to Dec
ANALYSIS: Graphic. Power spectral analysis (individual).
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
PEAK: epileptics 1400-2000; controls 1800-2000
TROUGH: epileptics 2400-0500; controls 0300-0500
RANGE:
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER: epileptic patients showed more inconsistent results.
LIMITATIONS: no cosinor analysis

APFELBAUM, REINBERG, LACATIS (1976)
SUBJECTS: N=36 healthy, obese. Age: 18-25 yr Gender: females
VARIABLE(S): HR
METHODS: FREQUENCY: 6 hr intervals (06-12-18-24)
LENGTH: see measurement
MEASUREMENT: self rating of radial pulse. Time 1: while eating normally - 08, 12, 20 (24-48 hr) and (N=7). Time 2: caloric restriction, protein diet for 3 weeks; N=6 1, wk, 4 equal meals 08, 12, 16, 20. Time 3: N=24, 1 wk 1 meal 08. Time 4: N=24, 1 wk 1 meal 20. Lights on 0730, lights off 2330.
TIME OF YEAR:
ANALYSIS: Cosinor. Ref to sleep: midsleep
FINDINGS: PERIOD: Yes X, No ___ $p<.05$ for Times 1, 2, 4 only
LENGTH OF PERIOD: circadian
ACROPHASE: Time 1: 1601 (1401, 1800); Time 2: 1718 (1218, 2158); Time 3: 1452; Time 4: 1724 (1318, 2131)
AMPLITUDE: Time 1: 7.7 (4.5, 10.9); Time 2: 3.2 (1.0, 5.4); Time 4: 2.3 (0.7, 3.8)
MESOR: Time 1: 75.2 ± 3.2; Time 2: 78.5 ± 1.3; Time 3: 87.2 ± 6.7; Time 4: 81.5 ± 0.9
SHAPE OF WAVEFORM: sinusoidal
OTHER: no shift in acrophase or amplitude with different meal times
LIMITATIONS: none noted

WILSON, KRIPKE, MCCLURE, GREENBURG (1977)
SUBJECTS: N=10 surgical ICU patients Age: 42-77 yr (57 yr)
Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: continuous. Averaged at 5 min intervals
LENGTH: 12-28 hr
MEASUREMENT: ECG - HR. ICU darkened from 2200-0600. Unknown when patients slept. Most data were collected from 1800-0600.
TIME OF YEAR: over 2 months
ANALYSIS: Graphic. Spectral analysis for 90 min period. Autovariance function computed for 0-36 lags (3 hr) - variance spectrum derived.
FINDINGS: PERIOD: Yes ___, No X
LENGTH OF PERIOD:
PEAK:
TROUGH:
RANGE:
MEAN:
SHAPE OF WAVEFORM:
OTHER: no 90-100 min period seen
LIMITATIONS: unknown when patients slept. No cosinor analysis. 12-28 hr data not provided. Used an artifact screening algorithm that dicarded every 5 min the high and low run; thus 3 mins were averaged every 5 minutes.

MURPHY, RANDLE, WILLIAMS (1977)
SUBJECTS: N=4 healthy students Age: 18-21 yr Gender: male
VARIABLE(S): HR
METHODS: FREQUENCY: 3 hr intervals
LENGTH: 24 hr X 7
MEASUREMENT: HR recorded manually - Pulsemeter using a finger sensor, lights on and off were staggered at 45 min increments.
TIME OF YEAR:
ANALYSIS: single harmonic. Autocorrelograms and periodograms
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24.5 hr (p.003)
PEAK: 1800
TROUGH: 0700
RANGE:
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: no cosinor analysis

BRODSKY, WU, DENES, KANAKIS, ROSEN (1977)
SUBJECTS: N=50 medical students without CVD Age: 23-27 yr (cau) Gender: males
VARIABLE(S): HR & R
METHODS: FREQUENCY: continuously
LENGTH: 24 hr
MEASUREMENT: ECG - HR taped (Avionics). Normal daily routine. No medications. Sleep ranged from 4.5 to 10 hr. Diaries kept.
TIME OF YEAR:
ANALYSIS: frequency only
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK: HR increased while awake
TROUGH: HR decreased while asleep
RANGE: 59-87
MEAN: 73 ± 7 (awake 80 ± 7; asleep 56 ± 6)
SHAPE OF WAVEFORM:
OTHER: waking period HR - 53 ± 6 to 141 ± 17. Sleeping period 43 ± 5 to 86 ± 9. 12% sinus bradycardia < 40 beats/min during sleep. 50% had episodes of marked sinus arrhythmia (adjacent cycle lengths change by >100%.) 68% had sinus pauses of more than 1.50 sec during sleep. 6% had Type I 2^{o} HB transiently during sleep. 56% had PACs. Only 1 subject had >100 PACs in 24 hr. 50% had PVCs. Only 1 subject had >50 PVCs in 24 hr. N=8 more with sleep. N=16 more while awake. N=1 equal. N=1 VT during sleep.
LIMITATIONS: no hourly data presented

RUDOLF & TOLLE (1977)
SUBJECTS: N=26 endogenous depressives and N=10 neurotic depressives Age: N=26 Gender: N=26, 3 x more females
VARIABLE(S): HR
METHODS: FREQUENCY: 2 hr at night; 4 hr during day
LENGTH: 3-24 hr periods before, during, after sleep deprivation
MEASUREMENT: in-patients, "Clinical - Manual" methods for HR.
TIME OF YEAR: 1974
ANALYSIS: Wilcoxon test and Mann Whitney U
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr
PEAK: 0800-1200
TROUGH: 2400-0400
RANGE: N=26, 8.7-15.1; N=10, 10.2-14.6
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER: decreased amplitude with increased sleep deprivation with endogenous depressives.
LIMITATIONS: no cosinor analysis

SMOLENSKY, BERGMAN, BARNARD, BECK, KRAFT (1977)
SUBJECTS: N=3 total (single) and N=1 double heart transplantation patients Age: 60-80 yr Gender:
VARIABLE(S): HR
METHODS: FREQUENCY: continuous. At 15 min intervals - 1 min averaged.
LENGTH: 72 hr
MEASUREMENT: slept 2200-0700 Houston; 2230-0600 Capetown in hospital. Assumed to be day active. ECG-HR taped (Holter) or recorded directly.
TIME OF YEAR:
ANALYSIS: Cosinor: individual and group (2-37 hr used)
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr single, donor
ACROPHASE: single: 1656 (0956, 2100) Donor.
AMPLITUDE: single: 7.7 (.1, 15.4) Donor.
MESOR: single: 90.1 ± 12.8 Donor.
SHAPE OF WAVEFORM: sinusoidal
OTHER: The double heart patient had significant periods of 29 hr (R=recipient) and 24 hr (D=donor). Ultradian rhythms of 2.3 hr (R), 2.4 hr (D), 2.9 hr (D), 3.5 hr (D & R), 3.9 hr (R), 4.0 hr (D), 5.0 hr (R & D), 6.0 hr (D).
LIMITATIONS: there was incomplete reporting of HR data. Patients were assumed to be data active.

PICKERING, GOULDING, COBERN (1977)
SUBJECTS: N=31 untreated patients with PVCs (N=17, no cardiac disease; N=11, CHD; N=3 MVP) Age: N=17, 44 yr; N=11, 61 yr; N=3, 51 yr Gender: N=21 males, N=10 females
VARIABLE(S): HR & PVCs
METHODS: FREQUENCY: continuous
LENGTH: 24hr x 1 (N=15 24 hr x 2)
MEASUREMENT: ECG - HR & R taped (Medilog). Outside of hospital. Usual activities. No antiarrhythmic medications
TIME OF YEAR:
ANALYSIS: scanner used. Individual and group. Graphic. T-test. Average hourly PVCs between 0100 and 0400 (all patients were asleep) compared with average hourly PVCs between 0900 and 1400 (all patients were awake)
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
PEAK: HR - 0830, 1200, 1600, 1930; PVCs - 0830 to 1600
TROUGH: HR and PVCs decreased with sleep. p<.001 (absolute frequency). p<.05 (relative to 100 beats per min)
RANGE: HR - 31 to 39 ± 16
MEAN:
SHAPE OF WAVEFORM: sinusoidal with 3-4 peaks during day
OTHER: N=8 disappearance of PVCs during night. N=22 reduction in PVCs during night. N=1 increased in PVCs at night. Individuals were consistent on retesting.
LIMITATIONS: no cosinor analysis

MILLER-CRAIG, BISHOP, RAFTERY (1978)
SUBJECTS: N=20 increased B/P; N=5 controls Age: 34-72 yr (54 yr); 19-43 yr (29 yr) controls Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: continuous. Average per hour calculated.
LENGTH: 48 hr
MEASUREMENT: outpatient. ECG - HR taped (Medilog)
TIME OF YEAR:
ANALYSIS: Graphic.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
PEAK: 1230 (increased B/P); 1300 (control)
TROUGH: 2240-0700 (increased B/P); 0230-0430 (control)
RANGE: 70-108 (increased B/P); 65-101 (control)
MEAN:
SHAPE OF WAVEFORM: sinusoidal. Waveforms for both groups were similar
OTHER: increased on awakening (0600-0900)
LIMITATIONS: no cosinor analysis

STEINBACH, EDER, GLOGAR, JOSKOWICZ, WEVER (1978)
SUBJECTS: N=29 patients Age: Gender:
VARIABLE(S): PVCs
METHODS: FREQUENCY: continuous and averaged for 6 hr segments
LENGTH: 24 hr
MEASUREMENT: ECG - HR taped
TIME OF YEAR:
ANALYSIS: Mulipass scanning used to interpret PVCs
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: circadian in 77% of the patients
PEAK:
TROUGH: during night
RANGE:
MEAN:
SHAPE OF WAVEFORM:
OTHER:
LIMITATIONS: no cosinor analysis

GOLDBERG, RAFTERY, CASHMAN, STOTT (1978)
SUBJECTS: N=41 ambulant untreated hypertensives Age: 23-66 yr (47 yr) Gender: N=29 males; N=12 females
VARIABLE(S): HR
METHODS: FREQUENCY: continuous and averaged at 3 hr intervals
LENGTH: 48 hr
MEASUREMENT: N=26 in patients; N=15 outpatients. Diaries kept. ECG - HR tapes.
TIME OF YEAR:
ANALYSIS: scanner used. Descriptive statistics
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr
PEAK: 0900-1900
TROUGH: during the night
RANGE: 19.3 ± 16.5
MEAN: day 59-130 (93 ± 19); night 54-94 (74.1 ± 8.9)
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: no cosinor analysis

ADEY et al. (1978)
SUBJECTS: N=189 health adults Age: 20-70 yr, 44 yr
Gender: N=130 males; N=59 females
VARIABLE(S): HR & R
METHODS: FREQUENCY: continuous
LENGTH: 24 hr
MEASUREMENT: ECG - HR taped (Avionics)
TIME OF YEAR:
ANALYSIS: scanner used. Graphic.
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr
PEAK: 1400-1500
TROUGH: between 2400-0600
RANGE:
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER: 37% had arrhythmias. 16% had ventricular (6.3% serious). 10.5% had supraventricular. 10.5% had combined.
LIMITATIONS: 85% agreement by 2 ECG scanners. No cosinor analysis.

KENNEDY, CHANDRA, SAYTHER, CARALIS (1978)
SUBJECTS: N=67 with CHD; N=23 NLs Age: patients mean age 56-58 yr Gender:
VARIABLE(S): PVCs
METHODS: FREQUENCY: continuous
LENGTH: 48 hr
MEASUREMENT: ECG - HR (Avionics-Holter). Fully Ambulatory. Diary kept.
TIME OF YEAR:
ANALYSIS: scanner used. Frequency only.
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK: most patients had increased PVCs with mild to moderate exercise (50-80%)
TROUGH:
RANGE:
MEAN:
SHAPE OF WAVEFORM:
OTHER: 87% had ventricular ectopy (patients) - multifocal or repetitive pattern in 62% and PVCs > 60/hr in 30%. 35% had ventricular ectopy (NLs). 8 to 26% (patients) had maximal ventricular ectopy with sleep.
LIMITATIONS: gender unknown. No cosinor analysis.

KAWASAKI, MATSUOKA, HALBERG, E., HALBERG, F. (1978)
SUBJECTS: N=1 Japanese (J), healthy subject; N=1 North American (A), healthy subject Age: 34 yr (J), premenopausal (A) Gender: females
VARIABLE(S): HR
METHODS: FREQUENCY:
LENGTH: 96 days/few months
MEASUREMENT: self measured pulse (site unknown)
TIME OF YEAR:
ANALYSIS: Cosinor: single
FINDINGS: PERIOD: Yes _X_, No ___ $p<.001$
LENGTH OF PERIOD: 24 hr; 24 and 29 days
ACROPHASE: circadian (J) 2066 (1744, 2244); (A) 2220 (0140, 1900). Frequency of HR measurement unknown
AMPLITUDE: circadian. J-3.09 (1.36, 4.8); A-1.95 (0.84, 3.06)
MESOR: J-81 ± 0.53; A-78.3 ± 0.37
SHAPE OF WAVEFORM: sinusoidal
OTHER: (J) Circatrigintan (29 days). Range 27-30 days. Acrophase HR=-359° (360° = 29 days, 12° = 1 day). Amplitude 5. Mesor 82 ± 0.5. (A) Circatrigintan (24 days). Acrophase HR=-229°. Amplitude 2.46. Mesor 78.3 ± 0.34.
LIMITATIONS: small number of subjects. Unknown if subjects were day active. Frequency of HR measurement unknown.

MORGANROTH, MICHELSON, HOROWITZ, JOSEPHSON, PEARLMAN, DUNKMAN (1978)
SUBJECTS: N=15 stable CVD patients with > 30 PVCs/hr over 24 hr
Age: 38-68 yr (56 ± 10 yr) Gender: N=14 males; N=1 female
VARIABLE(S): PVCs
METHODS: FREQUENCY: continuous
LENGTH: 3 - 24 hr periods. N=5 underwent repeated 72 hr monitoring 3 months later.
MEASUREMENT: ECG - taped (Avionics). No antiarrhythmic medications. Diaries kept.
TIME OF YEAR:
ANALYSIS: ANOVA: 4 and 5 factor nested
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK: during the day
TROUGH: during sleep, 2400 to 0800
RANGE:
MEAN: 37-1,801 PVCs/hr
SHAPE OF WAVEFORM:
OTHER: 48% variation in frequency of PVCs in individuals occurred hour to hour. 23% variation in frequency of PVCs in individuals occurred day to day. 37% variation in frequency of PVCs in individuals occurred between 2 sets of 3 day monitoring. Arrhythmia frequency decreased 2400 to 0800.
LIMITATIONS: no cosinor analysis

FLORAS, JONES, JOHNSTON, BROOKS, HASSAN, SLEIGHT (1978)
SUBJECTS: N=5 NLs, N=14 increased B/P Age: Gender:
VARIABLE(S): HR
METHODS: FREQUENCY: continuous. Averaged at 2 min intervals
LENGTH: 24 hr
MEASUREMENT: ambulant ECG. Voice recorder and digital clock to record events.
TIME OF YEAR:
ANALYSIS: Graphic. Ref to sleep: arousal (0519 to 0836)
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK: with arousal
TROUGH: with sleep
RANGE: 69 ± 3.2 to 80 ± 3.9
MEAN:
SHAPE OF WAVEFORM:
OTHER:
LIMITATIONS: no cosinor analysis. No other HR data presented. Gender and age unknown.

PICKERING, JOHNSTON, HONOUR (1978)
SUBJECTS: N=12 patients with untreated PVCs Age: 35-74 yr (49 yr) Gender: N=10 males; N=2 females
VARIABLE(S): PVCs & HR
METHODS: FREQUENCY: continuously
LENGTH: 24 hr
MEASUREMENT: ECG-HR & R. EEG-sleep eye movements measured. Slept at home.
TIME OF YEAR:
ANALYSIS: Frequency only
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK: activity period (mild exercise)
TROUGH: sleep
RANGE: HR 61.2 ± 12.7 to 75.5 ± 9.5 (19% decreased with sleep). PVCs 2.4 ± 3.4/100 beats to 6.4 ± 6.1/100 beats (69.2% decreased with sleep)
MEAN:
SHAPE OF WAVEFORM:
OTHER: majority had no marked differences between HR and PVCs at different levels of sleep. N=2 increased PVCs with REM periods. N=1 increased PVCs during stages 3 and 4. Decreased PVCs as HR decreased during the night. Increased PVCs at onset of sleep. Multifocal and paired PVCs occurred frequently during wakefulness in N=4.
LIMITATIONS: no cosinor analysis

MANN, MILLER-CRAIG, ALTMAN, MELVILLE, RAFTERY (1979)
SUBJECTS: N=12 with mild or moderate untreated hypertension
Age: 38-62 yr (54 yr) Gender:
VARIABLE(S): HR
METHODS: FREQUENCY: continuous. Averaged hourly.
LENGTH: 24 hr x 2 (2-4 month inbetween)
MEASUREMENT: ECG-HR. Outpatients. Metoprolol started between 2 measurement periods.
TIME OF YEAR:
ANALYSIS: time of awakening used as reference. Graphic.
FINDINGS: PERIOD: Yes X, No ___ for both times
LENGTH OF PERIOD: 24 hr
PEAK: 1230-1730
TROUGH: 2400-0700
RANGE: 69-99 (Time-1); 55-75 (Time-2)
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER: HR decreased throughout day.
LIMITATIONS: no cosinor analysis

WINGET, DE ROSHIA, SANDLER (1979)
SUBJECTS: N=8 healthy subjects Age: 35-45 yr Gender: females
VARIABLE(S): HR
METHODS: FREQUENCY: 30 min
LENGTH: 23 days
MEASUREMENT: 9 days - ambulatory control; 9 days CBR; 5 days recovery. Controlled environment. 16L:8D (lights on at 0700). HR-ECG.
TIME OF YEAR:
ANALYSIS: harmonic analysis. R.A. Fisher Test - significance of rhythm amplitudes. Graphic.
FINDINGS: PERIOD: Yes X, No ___ $p<.01$ for all three periods
LENGTH OF PERIOD:
ACROPHASE: 8.1-8.4 hr after awakening (0700)
AMPLITUDE:
MEAN: 74.01 ± 1.74 to 80.16 ± 1.2
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: no cosinor analysis

SCHAEFER, KERR, BUSS, HAUS (1979)
SUBJECTS: N=11 on submarine patrols Age: Gender:
VARIABLE(S): HR
METHODS: FREQUENCY: 4 hr interval
LENGTH: 2-18 hr
MEASUREMENT: Control = 5 days before patrol. N=11 1st patrol - 18 hr watch (6hr on 12 hr off) (1-15 days). N=6 2nd patrol - N=3 - 18 hr watch, N=3 - 24 hr watch (41-52 days)
TIME OF YEAR:
ANALYSIS: Cosinor
FINDINGS: PERIOD: Yes X, No ___ $p<.05$
LENGTH OF PERIOD: 18 hr (for those on 18 hr watch schedule); 24 hr (for those on 24 hr watch schedule)
ACROPHASE: Control - 2000 (1440, 2400); 1st patrol - 2000; 2nd patrol - 2200
AMPLITUDE: Control - 4.44 ± 4.39; 1st patrol - 3.07; 2nd patrol - 3.78
MESOR: Control - 73.5 ± 6.15; 1st patrol - 70.02 ± 8.11; 2nd patrol - 73.00 ± 8.93
SHAPE OF WAVEFORM: sinusoidal
OTHER: additional 12 hr, 36 hr, and 48 hr cycles were detected in both patrols
LIMITATIONS: raw data not presented. Unknown when lows occurred. Age and gender unknown.

CHRIST (1979)
SUBJECTS: N=8 tetraplegic subjects Age: 37.5 yr Gender:
VARIABLE(S): HR
METHODS: FREQUENCY: 30 min
LENGTH: 24 hr
MEASUREMENT: cord injury between C_4 & C_7. No restriction on routine. N=5 CBR; N=3 wheelchairs. Pulses counted.
TIME OF YEAR: Mar 1-2, 1974
ANALYSIS: autocovariance. Graphic (individual).
FINDINGS: PERIOD: Yes X, No ___ (all but one subject)
LENGTH OF PERIOD: 20.5 to 24 hr
PEAK: day
TROUGH: night
RANGE: 58-106
MEAN:
SHAPE OF WAVEFORM: sinusoidal with many peaks
OTHER: The remaining one subacute tetraplegic subject demonstrated no circadian rhythmicity of heart rate. It is postulated that central denervation of the heart from the sympathetic division of the autonomic nervous system in cervical cord injury results in loss of circadian rhythmicity in heart rate until the vagus of the parasympathetic division obtains control, sympathetic spinal cord centers re-establish control, or an orderly interaction of both occurs.
LIMITATIONS: no cosinor analysis. Gender unknown.

APPELHOFF, FENTROP, HARTUNG, LIGHT, STELLING (1979)
SUBJECTS: N=4 healthy subjects Age: 20-28 yr Gender: males
VARIABLE(S): mean velocity (index of CO), HR, & SV
METHODS: FREQUENCY: 2-3 hr
LENGTH: 72 hr
MEASUREMENT: slept at night. In lab. Aortic blood velocity was measured by transcutaneous aortovelography
TIME OF YEAR:
ANALYSIS: meals excluded. Graphic. Paired T.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
PEAK: day
TROUGH: night
RANGE: CO-9% decrease at night; HR decreased 2% at night; SV decreased 15% at night.
MEAN:
SHAPE OF WAVEFORM:
OTHER: meals and activity increased HR, SV, & CO.
LIMITATIONS: very little data reported in abstract. No cosinor analysis.

MILLER, HELANDER (1979)
SUBJECTS: N=2, healthy subjects Age: 33 and 34 Gender: males
VARIABLE(S): CO, SV & HR
METHODS: FREQUENCY: 1 hr intervals
LENGTH: 48 hr in laboratory
MEASUREMENT: CO measured with impedance plethysmographic method (SV) and HR. HR measured with ECG, lead II. Day active. 48 hr period in laboratory. Normal days of sedentary work (0830-1730). Subject B was awake during night 2 and slept during night 1. Subject A slept during night 2 and was awake during night 1. No alcohol, nicotine, or physical exercise. CO measured every hour at end-expiration after 10 min of quiet sitting (when awake).
TIME OF YEAR: September 26-28, 1977
ANALYSIS: Graphic: chronograms. Cosinor
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr with and 24 hr without sleep.
ACROPHASE: A - CO=2012, SV=0430, HR=1836 (awake for 24 hr). B - CO=2254, SV=0048, HR=1942 (awake for 24 hr).
AMPLITUDE: A-CO=.37, SV=3.9, HR=6.4. B-CO=.54, SV=9.3, HR=16.
MESOR: A - CO=5.56 ± .35, SV=90 ± 7, HR=62.1 ± 6.4. B - CO=7.19 ± .72, SV=155 ± 13.2, HR=46.4 ± 2.7.
SHAPE OF WAVEFORM: sinusoidal
OTHER: CO was affected by meals causing 1-2 hr peak in CO (due to increased SV). CO decreased during sleep (due to decreased SV). CO and HR decreased during the night even when person did not sleep.
LIMITATIONS: time of data collection varied between subjects. Small N. Cosinor analysis only on 24 hr data when subjects stayed awake.

MANN, MILLER-CRAIG, MELVILLE, BALASUBRAMANIAN, RAFTERY (1979)
SUBJECTS: N=3 NLs, N=7 (increased B/P) Age: 29-64 yr (44)
Gender: N=8 males; N=2 females
VARIABLE(S): HR
METHODS: FREQUENCY: continuous. Hourly averages.
LENGTH: 48 hr
MEASUREMENT: ECG-HR. Random sequence of bedrest for 24 hr in the hospital and activity for 24 hr with normal sleep (outside the hospital). Day active.
TIME OF YEAR:
ANALYSIS: Ref to sleep: time of awakening. T-tests used for between-day differences in mean values.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
PEAK: 1400 - ambulant day; 0930 BR day
TROUGH: 0530
RANGE: ambulant day - 26 beats (37%); BR day - 11 beats (17%)
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER: lowest during bedrest (2400-0700)
LIMITATIONS: no cosinor analysis

MICHELSON, MORGANROTH (1980)
SUBJECTS: N=20 stable patients with cardiac disease and >30 PVCs/hr Age: 58 ± 9 yr, 39-71 yr Gender: N=16 males; N=4 females
VARIABLE(S): PVCs
METHODS: FREQUENCY: continuous
LENGTH: 24hr x 4 days
MEASUREMENT: ECG taped. (Avionics) N=2 monitored for a second 4 day period. No antiarrhythmic drugs. Outpatient activity routines kept constant.
TIME OF YEAR:
ANALYSIS: ANOVA 4-factor nested.
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK:
TROUGH: 2400-0800
RANGE: 35-1791 PVC/hr
MEAN: 438 ± 523 PVC/hr
SHAPE OF WAVEFORM:
OTHER: N=20 had PVCs and N=14 had VT. 30% of variation explained by hourly rates of PVCs $p<.05$. 70.6% of variation explained by hourly rates of VT. 64.2% of variation explained by hourly rates of couplets. 20% decreased in complex arrhythmias with sleep ($p<.01$)(2400-0800).
LIMITATIONS: no cosinor analysis

TARTINI, MOCCETTI, RIVA, BELLI (1980)
SUBJECTS: N=245 with MVP (N=52 chosen randomly) Age: 35.5 ± 16.9 yr (18-62 yr) Gender: 2-3 females to 1 male
VARIABLE(S): HR & PVCs
METHODS: FREQUENCY: continuously
LENGTH: 24hr
MEASUREMENT: ECG-HR taped (Holter)
TIME OF YEAR:
ANALYSIS:
FINDINGS: PERIOD: Yes X, No ___ PVCs
LENGTH OF PERIOD: 24hr
PEAK: PVCs during activity
TROUGH:
RANGE:
MEAN:
SHAPE OF WAVEFORM: HR - sinusoidal
OTHER:
LIMITATIONS: no cosinor analysis. HR data not presented.

ASLANIAN, ADAMIAN, GRIGORIAN, BAGDASSARIAN, ASSATRIAN (1980)
SUBJECTS: N=141 patients with CHD; N=25 controls Age: Patients: 30-70 yrs (50.8 ± 0.7 yr); Control: 37-52 yr (42.3 ± 0.4 yr) Gender:
VARIABLE(S): HR
METHODS: FREQUENCY: 3 hr intervals
LENGTH: 24 hr
MEASUREMENT: slept 2230 to 0730. Ate every 3 hr. Studied on 2nd and 3rd day after hospitalization. No medications. ECG-HR, 12 leads.
TIME OF YEAR:
ANALYSIS: Graphic. Cosinor: individual and group
FINDINGS: PERIOD: Yes X, No ___ p<.05 (group)
LENGTH OF PERIOD: 24 hr
ACROPHASE: Controls - 1800 (1315, 2000); Patients - 1500 (1230, 1700)
AMPLITUDE: Controls = 2.6 (.9, 4.4); Patients = 2.9 (1.8, 3.9)
MESOR: Controls - 83.8 ± 2.3; Patients - 70 ± 1.2
SHAPE OF WAVEFORM: sinusoidal
OTHER: individual cosinor analysis: significant circadian rhythm in N=27 patients and N=6 controls.
LIMITATIONS: gender unknown. Time of year of study unknown.

CLENCH, BARTON, LENART, MURILLO, SCHULL (1980)
SUBJECTS: N=13 healthy Aymara Indians who live at high altitude
Age: 24-46 yr Gender: N=9 males; N=4 females
VARIABLE(S): HR
METHODS: FREQUENCY: continuous
LENGTH: 24 hr
MEASUREMENT: ECG-HR taped (Medilog). Normal daily activities. Slept 2100-0600.
TIME OF YEAR: April 6-20, Autumn in Bolivia
ANALYSIS: Cosinor: single and group
FINDINGS: PERIOD: Yes X, No ___ p<.001
LENGTH OF PERIOD: 24 hr
ACROPHASE: 1454 (1238, 1648)
AMPLITUDE: 12.07 (5.47-18.78)
MESOR: 64.19 ± 2.03
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: none noted

KELLEROVA, VICENIK, CINGELOVA (1980)
SUBJECTS: N=6 healthy subjects Age: Gender:
VARIABLE(S): R-R intervals
METHODS: FREQUENCY: 3 hr intervals
LENGTH: 24 hr
MEASUREMENT:
TIME OF YEAR:
ANALYSIS: Histogram. Kolmogorov-Smirnov test
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
PEAK:
TROUGH: evening
RANGE:
MEAN:
SHAPE OF WAVEFORM:
OTHER:
LIMITATIONS: no cosinor analysis. Age and gender unknown. Measurement details not provided in abstract.

SENSI et al. (1980)
SUBJECTS: N=13 ambulatory patients with CHD Age: 46-69 yr
Gender:
VARIABLE(S): PVCs
METHODS: FREQUENCY: continuous and averaged over an hour
LENGTH: 24 hr
MEASUREMENT: synchronized for a week according to: L/D - 0700/2200; meals at 0800, 1300, 2000. ECG-PVCs.
TIME OF YEAR:
ANALYSIS: Cosinor
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
ACROPHASE: 1534 (1048, 1913)
AMPLITUDE: 64.73 ± 29.1 PVC/hr
MESOR: 60.14 ± 17.82 PVCs/hr
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: gender unknown

DOMENICHELLI, et al. (1980)
SUBJECTS: N=39 patients with MI Age: Gender:
VARIABLE(S): HR & PVCs
METHODS: FREQUENCY: continuous
LENGTH: 24 hr
MEASUREMENT: ECG-HR & R taped (Holter)
TIME OF YEAR:
ANALYSIS: Cosinor.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
ACROPHASE: controls: 1653 (1551, 1920); patients: 1731 (1628, 1840)
AMPLITUDE: patients: 13.7
MESOR: patients: 68.24 ± 3.18
SHAPE OF WAVEFORM:
OTHER: PVCs - Acrophase 1524. N=2 had CHB - atrial rate acrophase = 1140; ventricular rate acrophase=1227.
LIMITATIONS: incomplete reporting of cosinor analysis.

MORRISON, KUMAR, PORTAL, ABER (1981)
SUBJECTS: N=44 patients with acute MI Age: 59.7 ± 7.9 yr
Gender: N=28 males; N=16 females
VARIABLE(S): HR & R
METHODS: FREQUENCY: continuous and averaged every 60 min
LENGTH: three-24 hr periods
MEASUREMENT: before, during, and after discharge (10-14 days after MI). ECG (Medilog).
TIME OF YEAR:
ANALYSIS: Graphic. T-test between high and low values. Linear regression analysis.
FINDINGS: PERIOD: Yes X, No ___ p<.001-HR
LENGTH OF PERIOD: 24 hr (all three times)
PEAK: 1200-1800
TROUGH: 2400-0600
RANGE: 72.8 ± 1.2 - 77.4 ± 1.3
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER: frequency and grade of PVCs lower during sleep (NS)
LIMITATIONS: no cosinor analysis

AHNVE, THEORELL, AKERSTEDT, FROBERG, F. HALBERG (1981)
SUBJECTS: N=12 healthy subjects Age: 19-30 yr Gender: males
VARIABLE(S): HR & SV (as judged by ballistocardiography - IJ amplitude)
METHODS: FREQUENCY: 3 hr
LENGTH: 64 hr - kept awake
MEASUREMENT: isolated from external time cues. Constant environment. Activity was sedentary. Meals evenly distributed throughout day. SV (Ballistocardiography). Arrived 1 day prior to study. Awoke at 0710 and study began at 0800. ECG-HR. 4 persons per group.
TIME OF YEAR:
ANALYSIS: Cosinor: single and group. ANOVA. Graphic.
FINDINGS: PERIOD: Yes X, No ___ (p=.006)
LENGTH OF PERIOD: 24 hr
ACROPHASE: 2108 (16.56-0100)
AMPLITUDE: 1.63 (.47-2.93)
MESOR: 54.98 mm
SHAPE OF WAVEFORM:
OTHER: heart rate showed no significant rhythmicity. Constant conditions largely obliterate the circadian rhythm of HR seen under nythemeral conditions. Sleep/wake cycle is probably responsible for part of the amplitude.
LIMITATIONS: HR may need to be sampled at an interval less than 3 hr to detect change. IJ corresponds to LV contractility, only one component of SV.

ALBONI, et al. (1981)
SUBJECTS: N=12 NLs; N=11 patients with intermittent bradycardia; N=9 patients with persistent bradycardia; N=7 2:1 SA block Age: N=12 9-74 yr (48.5); N=11 22-68 yr (48.0); N=9 38-76 yr (58.4); N=7 44-83 yr (65.5) Gender: N=12 - males = 7; females = 5; N=11 males = 6; females = 5; N=9 males =6; females = 3; N=7 males=4; females =3
VARIABLE(S): HR
METHODS: FREQUENCY: continuous and averaged at 2 hr intervals
LENGTH: 24 hr
MEASUREMENT: ECG-HR taped (Holter)
TIME OF YEAR:
ANALYSIS: scanner used. Histograms. Cosinor. Used maximal, minimal, and modal frequency in NLs and in patients with intermittent bradycardia.
FINDINGS: PERIOD: Yes _X_, No ___ p<.003 in NLs and those with intermittent bradycardia
LENGTH OF PERIOD: 24 hr
ACROPHASE: NLs 1626-1651, N=11 (1631-1651)
AMPLITUDE: NLs (5.16 to 9.52); N=11 (3.87-4.83)
MESOR: NLs (72.24 ± 2.67 to 96.51 ± 3.96); N=11 (49.47 ± 2.19 to 58.70 ± 2.72)
SHAPE OF WAVEFORM: sinusoidal
OTHER: disappearance of circadian periodicity occurred as SN dysfunction was more severe.
LIMITATIONS: none noted

GOLOGORSKY, GRINENKO, VERESCHAGINA (1981)
SUBJECTS: N=79 surgical patients Age: Gender:
VARIABLE(S): HR
METHODS: FREQUENCY: 1 hr intervals
LENGTH: 25 hr
MEASUREMENT: during postanesthetic period and postoperatively
TIME OF YEAR:
ANALYSIS: Graphic: chronograms.
FINDINGS: PERIOD: Yes _X_, No ___ for some patients
LENGTH OF PERIOD: 6-7 hr, 13 hr
PEAK:
TROUGH:
RANGE: 6-7 hr (17-22%); 13 hr (17-26%)
MEAN:
SHAPE OF WAVEFORM:
OTHER: moderate disorders in circadian HR rhythm were found with general anesthesia.
LIMITATIONS: no cosinor analysis

HAUFF & SCHULTZE (1981)
SUBJECTS: N=10 (N=3 NLs; N=7 hypertensive) Age: Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: 15 min
LENGTH: 24 hr
MEASUREMENT: lights on 0600; dark 2200. HR (intraarterial telemetry) taped.
TIME OF YEAR:
ANALYSIS: Histograms. Graphic - chronograms. Harmonic analysis - spectrograms. Periodograms. Cosinor.
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr
ACROPHASE: 1330
AMPLITUDE: 6
MESOR:
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: incomplete reporting of cosinor analysis. Age of subjects unknown.

MILLER-CRAIG, MANN, BALASUBRAMANIAN, ALTMAN, RAFTERY (1981)
SUBJECTS: N=37 untreated hypertensives Age: 49.7 ± 10.4 yr
Gender: N=35 males; N=2 females
VARIABLE(S):
METHODS: FREQUENCY: continuous. Averaged hourly.
LENGTH: 24 hr
MEASUREMENT: ECG-HR taped (Medilog).
TIME OF YEAR:
ANALYSIS: scanner used. Graphic. T-Test.
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr
PEAK: day
TROUGH: sleep
RANGE: 65-102
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: no cosinor analysis. Unknown when subjects slept and ate.

ENDO, KOBAYASHI, YAMAMOTO, FUKUDA, SASAKI, OHTA (1981)
SUBJECTS: N=4 healthy subjects Age: 24-26 yr Gender: males
VARIABLE(S):
METHODS: FREQUENCY: 0600, 0800, 1200, 1900, 2100
LENGTH: 1 wk (CBR)
MEASUREMENT: regular sleep habits. No drugs. Could not speak. Lights on 0600; off at 2100. Meals 0700, 1200, 1700.
TIME OF YEAR:
ANALYSIS: Frequency only.
FINDINGS: PERIOD: Yes X , No ___
LENGTH OF PERIOD: 24 hr
PEAK: late afternoon
TROUGH: early morning
RANGE:
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: no measurements during the night. No cosinor analysis.

CLENCH, BARTON, SCHULL, ALEXANDER, THOMPSON, LAUGHLIN (1981)
SUBJECTS: N=24 healthy Eskimos Age: 18-69 yr living in Arctic tundra (60°N) Gender: N=21 males; N=3 females
VARIABLE(S): HR
METHODS: FREQUENCY: continuous. Averaged for 15 min.
LENGTH: 24 hr
MEASUREMENT: slept at will. LD12:12. ECG-HR taped (Medilog). Had electricity and could heat and light home.
TIME OF YEAR: March, 1979 (spring)
ANALYSIS: scanner used. Cosinor: group
FINDINGS: PERIOD: Yes X , No ___
LENGTH OF PERIOD: 24 hr
ACROPHASE: 1535 (1447, 1622)
AMPLITUDE: 8.78 (7.03, 10.53)
MESOR: 79.72 $\pm$ .53
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: none noted

BENOIT, FORET, MERLE, REINBERG (1981)
SUBJECTS: N=14 healthy, good sleepers Age: 20-23 yr
Gender: N=10 males/ N=4 females. (LS) N=7 slept > 9 hrs (Females=2); (SS) N=7 slept < 7 hr (Females=2). Stable sleep patterns for 10 years.
VARIABLE(S): HR
METHODS: FREQUENCY: 4 hr intervals while awake
LENGTH: 24 hr - 36 hr
MEASUREMENT: two sessions 2 weeks apart in an experimental lab. Session 1 - stayed awake for 24 hrs; Session 2 - stayed awake for 36 hrs. EEG used. 10 day-control period. Subjects counted pulse.
TIME OF YEAR: October to February
ANALYSIS: Graphic: chronograms. Cosinor: individual and group.
FINDINGS: PERIOD: Yes X , No ___ $p<.005$
LENGTH OF PERIOD: 24 hr
ACROPHASE: Control - SS 1548 (1442, 1700); LS 1648 (1606, 1742). After 24 hr of sleep deprivation - SS 1412 (1924, 1824). After 36 hr of sleep deprivation SS 1530 (1348, 1724).
AMPLITUDE: Control - SS 3.5 (2.3, 4.7); LS 5.4 (4.1, 6.8). After 24 hr of sleep deprivation - SS 3.3 (.2, 6.6). After 36 hr of sleep deprivation, SS 7.2 (3.2, 11.3).
MESOR: Control - SS 78.1 $\pm$ 0.4; LS 73 $\pm$ 0.5. After 24 hr of sleep deprivation - SS 79.6 $\pm$ 3.1. After 36 hr of sleep deprivation, SS 77.1 $\pm$ 3.9.
SHAPE OF WAVEFORM: sinusoidal
OTHER: LS had disturbed circadian rhythmicity after 24 hrs of sleep deprivation. After 36 hr of sleep deprivation the HR circadian rhythm returned (Acrophase 2000 (1400, 0030).
LIMITATIONS: none noted

E. HALBERG, F. HALBERG, SHANKARAIAH (1981)
SUBJECTS: N=2 (husband and wife) Age: 60-61 yr Gender: N=1 male with CHD; N=1 female
VARIABLE(S): HR
METHODS: FREQUENCY: 10 min intervals
LENGTH: 3 days (male); 26 days x 2 (female)
MEASUREMENT: HR (Nippon-Colin) automatic and printed out. Followed usual work/activity schedules.
TIME OF YEAR: October-November 1980
ANALYSIS: Graphic. Cosinor: single.
FINDINGS: PERIOD: Yes X, No ___ (for female only)
LENGTH OF PERIOD: 23.9 hr; 11.9 hr
ACROPHASE: 24 hr=1700 (1512, 1844); 12 hr=1432 (1828, 0020)
AMPLITUDE: (doubled) 24 hr 7.6 (4.2, 11.2); 12 hr 4.8 (1.4, 8.2)
MESOR: 64 (63, 65)
SHAPE OF WAVEFORM: sinusoidal
OTHER: for second set of 26 days - similar results were found. For the male - period was 23.8 hr. Acrophase = 1524 (1344, 1700). Amplitude = (double) 13.2 (7.8, 18.4). Mesor = 65 (63-67)
LIMITATIONS: none noted

TSUCHIYA et al. (1981)
SUBJECTS: N=8 untreated patients with increased B/P Age:
Gender:
VARIABLE(S): HR
METHODS: FREQUENCY: continuously. Averaged over 1 hr interval.
LENGTH: 24 hr
MEASUREMENT: no details presented
TIME OF YEAR:
ANALYSIS: Graphic.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
PEAK: 1300
TROUGH: 2400-0300
RANGE: 60-75
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER: N=3 on captopril decreased amplitude of HR circadian rhythm.
LIMITATIONS: no cosinor analysis. Gender and age unknown.

LEACH, RUSKIN, HALBERG (1981)
SUBJECTS: N=7 CHD; N=6 MVP; N=2 Aortic prostheses; N=5 other. Ambulatory patients with frequent ventricular ectopy
Age: Gender:
VARIABLE(S): ventricular ectopy and HR
METHODS: FREQUENCY: continuous
LENGTH: 24 hr
MEASUREMENT: diurnal wakefulness and nocturnal rest/sleep. ECG - HR & R. No antiarrhythmic drugs.
TIME OF YEAR:
ANALYSIS: Cosinor: single and group. Ref to sleep: local midnight
FINDINGS: PERIOD: Yes X, No ___ (P<.001 - HR; p=.239 - PVCs)
LENGTH OF PERIOD: 24 hr in HR (N=13) and PVC (N=9) individual analysis
ACROPHASE: HR: 1420 (1212, 1612); PVCs = 1744
AMPLITUDE: HR: 5.9 (3.5, 8.3); PVCs = 73
MESOR: HR - 72 ± 2; PVCs - 523 ± 112
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: age and gender unknown

KOSTIS et al. (1982)
SUBJECTS: N=101 with normal hearts Age: 16-68 yr (48.8yr)
Gender: N=51 males; N=50 females
VARIABLE(S): HR
METHODS: FREQUENCY: continuous
LENGTH: 24 hr
MEASUREMENT: ECG-HR taped (Avionics). Subjects slept 0100-0500. Awake and active 0900-1300. Sedendary, did not routinely exercise.
TIME OF YEAR:
ANALYSIS: scanner used. Correlation, Chi-square tests, and T-tests. Graphic.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
PEAK: 1000-1200
TROUGH: 0300-0500
RANGE: 8.4 ± 10.5
MEAN: 78.9 ± 8.8
SHAPE OF WAVEFORM: sinusoidal
OTHER: amplitude decreased with age.
LIMITATIONS: no cosinor analysis

ANDRESEN, VON LEITNER, WEGSCHEIDER, SCHRODER (1982)
SUBJECTS: N=42 patients with complex ventricular arrhythmias
Age: Gender:
VARIABLE(S): PVCs
METHODS: FREQUENCY: continuous
LENGTH: 3-24 hr periods
MEASUREMENT: ECG-HR taped
TIME OF YEAR:
ANALYSIS: Frequency
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK: varied with individual
TROUGH: varied with individual
RANGE:
MEAN:
SHAPE OF WAVEFORM:
OTHER: N=21 PVCs occurred equally day and night. N=21 PVCs had a regular pattern. 14 (33%) of them had the highest PVC frequency during day and 7 (17%) at night. 16 patients showed paired PVC. Only 50% (8 patients) showed a regular reproducible day-and-night rhythm during all three 24 hr periods. 6 of them had the highest frequency of paired PVCs during day and 2 at night. 23 patients showed a clearly recognizable relationship between PVC frequency and heart rate during all three periods. In 18, the PVC frequency ran parallel to the heart rate, but in 5 patients the PVC frequency ran contrary to the heart rate. In 16 patients, the PVC-frequency showed a constant relationship to both heart rate and time of day, 5 patients only evidenced a relationship to time of day and 7 only to heart rate.
LIMITATIONS: no cosinor analysis

VRANCIANU, et al. (1982)
SUBJECTS: N=10 male athletes; N=12 industrial workers Age: N=10, 18-25 yr; N=12, 22-29 yr GENDER: males
VARIABLE(S): HR
METHODS: FREQUENCY: 3 hr intervals
LENGTH: 30 hr (0700-1000 next day)
MEASUREMENT: (Resters) stayed together in a camp for 1 wk prior to study. Slept at same time. Workers worked 1 wk days and then 1 wk nights. Normal meals and rested or walked. (Workers) studied before, during and after different shifts. One was day and one was night. When on days, measures were at 0700, 1100, and 1500, and at night, measures were at 2300, 0300, and 0700. ECG-HR taped (Phillips).
TIME OF YEAR:
ANALYSIS: ANOVA. T-tests.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr for resters
PEAK: Resters - 1000
TROUGH: Resters 0400 (0100-0700)
RANGE: Resters 53.2 ± 6.2 to 63.8 ± 7.2
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER: workers - day shift, trough was at 0700 and peak was at 1100 for all three days. Workers - night shift, trough was at 0700 and peak was at 2300 for all three nights.
LIMITATIONS: no cosinor analysis

CARANDENTE, DE MATTEIS, MELIZZI, PITARI (1982)
SUBJECTS: N=1 healthy subject Age: 23 yr Gender: female
VARIABLE(S): HR
METHODS: FREQUENCY: continuos
LENGTH: 48 hr
MEASUREMENT: automatic heart rate measured. 5-sessions: 4 subsequent weekends and 1 month later. Each session: 48 hr 0800 Saturday - 0800 Monday. Slept. at night.
TIME OF YEAR: Mar 7 - April 30, 1981
ANALYSIS: Graphic: chronogram. Cosinor: single.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr for all 5 sessions
ACROPHASE: 1548 (1532, 1604) to 1752 (1716, 1828)
AMPLITUDE: 4.24 ± .87 to 8.33 ± .55
MESOR: 55 ± .39 to 66 ± 0.52
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: only one subject

PICKERING, HARSHFIELD, KLEINERT, BLANK, LARAGH (1982)
SUBJECTS: N=75 (N=25 NLs; N=25 borderline increased B/P; N=25 increased B/P) Age: NL, 31 ± 4 yr (26-43 yr); borderline increased B/P 31 ± 8 yr (17-44 yr); increased B/P 36 ± 8 (16-45 yr) Gender: NL N=19 males; N=6 females. Borderline increased B/P N=19 males; N=6 females. Increased B/P N=22 males; N=3 females.
VARIABLE(S): HR
METHODS: FREQUENCY: continuous
LENGTH: 24 hr
MEASUREMENT: ECG-HR taped (Avionics). Diaries kept. Usual activity. Scanner used.
TIME OF YEAR:
ANALYSIS: Difference between mean day and mean night
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK: day p<.01
TROUGH: night
RANGE: NL - 59 ± 6 to 78 ± 9. Borderline increased B/P - 66 ± 7 to 86 ± 10. Increased B/P - 76 ± 11 to 83 ± 8.
MEAN: NL - 75 ± 7. Borderline increased B/P - 78 ± 10. Increased B/P - 76 ± 11.
SHAPE OF WAVEFORM:
OTHER:
LIMITATIONS: no display of HR data. No cosinor analysis.

DRAYER, WEBER, DE YOUNG, WYLE (1982)
SUBJECTS: N=50 untreated increased B/P ambulatory patients. Age: 24-84 yr (50.9 ± 2.3 yr) Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: continuous. Averaged for 2 hr.
LENGTH: 24 hr
MEASUREMENT: ECG-HR taped. Daytime 0600-2200; nighttime 2200-0600.
TIME OF YEAR:
ANALYSIS: Graphic. T-Test, Correlation.
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr
PEAK: 1200-1400
TROUGH: during the night (0400-0600)
RANGE: 62 ± 1 to 89 ± 2
MEAN: 75 ± 2
SHAPE OF WAVEFORM: sinusoidal
OTHER: HR were lower in those over 55 yr (p<.01).
LIMITATIONS: no cosinor analysis

MESSERLI, et al. (1982)
SUBJECTS: N=13 age-matched normotensive subjects, N=11 patients with borderline hypertension, and N=10 patients with essential hypertension Age: 32 ± 2.7 yr to 33 ± 3 yr Gender: N=21 males; N=13 females
VARIABLE(S): HR & R
METHODS: FREQUENCY: continuous and averaged at 4 hr intervals (0900-1300, 1300-1700 etc.)
LENGTH: 24 hr
MEASUREMENT: ECG-HR taped (Avionics). 2100-0100 (TV time - could nap); 0100-0700 (slept). No medication. No coffee, tea, alcohol, bananas, oranges, cheeses, vanilla or cocoa allowed for 12 hr prior.
TIME OF YEAR:
ANALYSIS: scanner used. ANOVA.
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr
PEAK: 0900-1700
TROUGH: 0100-0700
RANGE: 63-86
MEAN: 75.1 ± 2.0 to 78.1 ± 2.0
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: no cosinor analysis. Arrhythmia frequency averaged for 24 hr. Time of day and incidence not given.

MARKIEWICZ, CHOLEWA, BECHLER (1982)
SUBJECTS: N=20 health subjects Age: 20-25 yr Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: 4 times in 24 hr (0900, 1600, 0200 after awakening, 0200 during all night activity)
LENGTH: 24 hr
MEASUREMENT: ECG-HR, lived under identical conditions in hospital. The 2nd 0200 measurement was obtained after the subjects were night active for 3 days and slept 8 hr during the day. Measurements were obtained after 30 min of rest.
TIME OF YEAR:
ANALYSIS: T-test, correlation, linear regression.
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr
PEAK: during day
TROUGH: during the night (p<.05)
RANGE: 59.2 ± 9.3 to 67.4 ± 9.7
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: only 4 measurements in 24 hr. No cosinor analysis.

ORTH-GOMER, F. HALBERG, SOTHERN, AKERSTEDT, THEORELL, CORNELISSEN (1982)
SUBJECTS: (1) N=42 with CHD, (2) N=32 with CHD risk factors, (3) N=29 NLs Age: 40-65 yr Gender: males
VARIABLE(S): PVCs
METHODS: FREQUENCY: continuous
LENGTH: 24 hr
MEASUREMENT: usual activities. Slept at night (2230-0630). ECG taped (Avionics). Diaries kept.
TIME OF YEAR:
ANALYSIS: Graphic: chronogram. Cosinor: single and group. Ref. to sleep: assumed to be similar. Other: harmonic analysis for periods shorter than 24 hr (3 hr-24 hr).
FINDINGS: PERIOD: Yes X, No ___ $p<.05$
LENGTH OF PERIOD: 24 hr
ACROPHASE: (1) 1244 (1012, 1536), (2) 1220 (0736, 1700), (3) 1236 (1009, 1412)
AMPLITUDE: (1) 41.5 (14.4, 68.8), (2) 42.3 (2.5, 82.2), (3) 83.3 (57.3, 109.7)
MESOR: (1) 10.19 ± 2.46/hr, (2) 11.55 ± 4.12/hr, (3) 4.97 ± 2.12/hr
SHAPE OF WAVEFORM: sinusoidal
OTHER: PVCs in 24% NLs; in 47% of risk group; in 38% of the CHD group. NLs showed periods of 6 hr and 3.43 hr.
LIMITATIONS: 1 single 24 hr period. Ignored other ultradian and all infradian components.

YANAGA, et al. (1982)
SUBJECTS: N=16 with PVCs Age: 58.9 ± 17.9 yr (31-85 yr)
Gender: N=7 males; N=9 females
VARIABLE(S): PVC & HR
METHODS: FREQUENCY: continuous
LENGTH: 24 to 72 hr
MEASUREMENT: ECG taped (Avionics). Day - 0600 to 1800; nights 1800 to 0600
TIME OF YEAR:
ANALYSIS: Lown's grading used. Scanner used. Frequency only.
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK: HR increased during the day
TROUGH: HR decreased during night
RANGE:
MEAN:
SHAPE OF WAVEFORM:
OTHER: N=2 had more PVCs at night. N=4 had more PVCs during day. N=10 had more PVCs during the day and night.
LIMITATIONS: no cosinor analysis

LEE, GILLUM, CORNELISSEN, KOGA, F. HALBERG (1982)
SUBJECTS: N=13 with increased B/P Age: Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: 1 hr interval
LENGTH: 24 hr x 3 months apart.
MEASUREMENT: ECG. No antihypertensive meds. At least 10% over ideal weight. Three stages: 1) reference, 2) sodium restriction (7 wks) break of 5 weeks, 3) weight reduction (7 wks). No cigarette smoking. No caffeine.
TIME OF YEAR: June through November
ANALYSIS: Cosinor: single
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
ACROPHASE: June = 1232; Aug = 1540; Nov = 1408
AMPLITUDE: June = 5.2 ± 4.3; Aug = 7.1 ± 2.9; Nov = 5.8 ± 3.1
MESOR:
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: unknown when subjects slept or whether they were day active. Age unknown.

RYZHIKOV, KUZMENKO, BULUEV (1982)
SUBJECTS: N=30 healthy subjects Age: 18-30 yr Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: 6 times a day (1200, 1600, 2000, 2300, 0400, 0800)
LENGTH: N=14 2-7 days separated by intervals of several days
MEASUREMENT: ECG-HR. Slept at night. Insolated chamber. 3 conditions: no magnetic field, mild, and strong.
TIME OF YEAR: 1 months time
ANALYSIS: Wilcoxon-Mann-Whitney
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
PEAK: 1600-2000
TROUGH: 0400
RANGE: 56-76
MEAN: 64.4 ± 1.5
SHAPE OF WAVEFORM: sinusoidal
OTHER: natural and artificial magnetic fields have an accelerating effect on the rhythm (shortening circadian rhythms)
LIMITATIONS: no cosinor analysis

STEINBACH, GLOGAR, WEBER, JOSKOWICZ, & KAINDL (1982)
SUBJECTS: N=87 patients over 1% PVC rate Age: Gender:
VARIABLE(S): PVCs
METHODS: FREQUENCY: continuous
LENGTH: 24 hr (N=10, 96 hr)
MEASUREMENT: ECG-R taped (Oxford, Medilot). Ambulatory.
TIME OF YEAR:
ANALYSIS: scanner used. Used PVC frequency in % of total beats. Log transformation of variation in PVCs frequency. Scheffe test. Graphic.
FINDINGS: PERIOD: Yes X, No ___ (in the majority of patients)
LENGTH OF PERIOD: 24 hr
PEAK: 0700-2400
TROUGH: 0000-0200
RANGE:
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER: N=10 - HR circadian rhythm in 7 subjects; PVC circadian rhythm in 4 subjects.
LIMITATIONS: no cosinor analysis. Gender and age unknown. Unknown when subjects slept or whether they were in the hospital.

GOULD, HORNUNG, MANN, BALASUBRAMANIAN, RAFTERY (1982)
SUBJECTS: N=20 patients with hypertension and N=9 patients with hypertension Age: N=20, 31-64 yr; N=9, 38-66 yr Gender: N=20, N=14 males,; N=6 females. N=9, N=5 males; N=4 females.
VARIABLE(S): HR
METHODS: FREQUENCY: continuous. Averaged at 1 hr intervals.
LENGTH: 36-48 hr before and after verapamil or nifedipine
MEASUREMENT: ECG-HR taped (Medilog, Oxford). Outpatients.
TIME OF YEAR:
ANALYSIS: Graphic.
FINDINGS: PERIOD: Yes X, No ___ (both groups)
LENGTH OF PERIOD: 24 hr
PEAK: 0800-1900
TROUGH: 0100-0600
RANGE: Before, 70-105; After, 60-90.
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER: circadian rhythm in HR occurred in both groups before and after drugs.
LIMITATIONS: no cosinor analysis. Unknown when subjects slept.

DERYAGINA, KRAEVSKII (1983)
SUBJECTS: N=60. (N=41 healthy subjects; N=19 patients with CHD) Age: NLs=21-45 yr, patients=28-55 yr Gender: NLs - N=26 males; N=15 females. Patients - N=11 males; N=8 females.
VARIABLE(S): HR
METHODS: FREQUENCY: 3 hours (0000, 0300, 0600, 0900, 1200, 1500, 1800, 2100)
LENGTH: 24 hr
MEASUREMENT: in hospital or during the course of a day outside hospital.
TIME OF YEAR:
ANALYSIS: Graphic. Descriptive statistics; correlation analysis. Differences between 3 hr intervals analyzed.
FINDINGS: PERIOD: Yes X, No ___ under working conditions
LENGTH OF PERIOD: 24 hr
PEAK: NLs=9 PM; Patients=3-6 PM
TROUGH: NLs=3-6 AM; Patients=6 AM
RANGE: NLs 69-77; Patients 71-83
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER: no significant difference in HR during the 24 hr period (at rest). Regular fluctuations were seen when measured during working conditions.
LIMITATIONS: no cosinor analysis. Means not reported.

LEACH, RUSKIN, F. HALBERG, SOTHERN (1983)
SUBJECTS: N=1 CHD patient in coma for 10 days after bypass surgery Age: Gender: male
VARIABLE(S): HR & PVCs
METHODS: FREQUENCY: continuous
LENGTH: 10 days
MEASUREMENT: ECG-HR & R
TIME OF YEAR:
ANALYSIS: Cosinor: single
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr for HR and longest runs of PVCs. 7 days for HR & PVCs and longest run of PVCs ($p<.001$). 96 hr for HR. 4.75 days for PVCs. 3.91 days for longest run of PVCs.
ACROPHASE:
AMPLITUDE:
MESOR:
SHAPE OF WAVEFORM:
OTHER:
LIMITATIONS: age unknown. Incomplete reporting of cosinor analysis.

DE LEONARDIS, CINELLI, CAPACCI, DE SCALZI, CITI (1983)
SUBJECTS: N=10 healthy subjects Age: 32-58 yr (44 ± 8 yr)
Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: 15 min intervals
LENGTH: 24 hr
MEASUREMENT: similar nychthemeral schedules. Slept between 2330-0645. No restriction on meals. ECG-HR taped (Cardiodyne).
TIME OF YEAR:
ANALYSIS: Cosinor
FINDINGS: PERIOD: Yes _X_, No ___ p<.0001
LENGTH OF PERIOD: 24 hr
ACROPHASE: 1613 (1456, 1800)
AMPLITUDE: 11 (6.5, 14.7)
MESOR: 76 ± 1
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: none noted

MANCIA, et al. (1983)
SUBJECTS: N=89 hospitalized patients (N=22 NL B/P; N=67 increased B/P) Age: Gender: N=55 males; N=34 females
VARIABLE(S): HR
METHODS: FREQUENCY: continuously. Average every 30 min.
LENGTH: 24 hr
MEASUREMENT: standardized living conditions. Night rest. Radial artery cannulated and minitape recorder used. No cardiovascular medications.
TIME OF YEAR:
ANALYSIS: Graphic. ANOVA. Coefficients of variance.
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr
PEAK: 1230
TROUGH: 2300-0430
RANGE:
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: no cosinor analysis. Age unknown.

F. HALBERG (1983)
SUBJECTS: N=35 day active Age: Gender:
VARIABLE(S): CO, SV, & HR
METHODS: FREQUENCY:
LENGTH:
MEASUREMENT:
TIME OF YEAR:
ANALYSIS: Cosinor.
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr
ACROPHASE: CO-1445 (N=1); SV-1430 (N=1); HR-1700 (N=35).
AMPLITUDE:
MESOR:
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: small sample size for CO & SV. No methods presented.

MONTAGUE, MC PHERSON, MACKENZIE, SPENCER, NANTON, HORACEK (1983)
SUBJECTS: N=45 with frequent PVCs (>100/day) Age: 2 weeks-62 yr (25 yr) Gender: N=21 males; N=24 females
VARIABLE(S): PVCs & HR
METHODS: FREQUENCY: continuous
LENGTH: 24 hr x 1. N=27 repeated 24 hr monitoring 8 months later (3-12 mo).
MEASUREMENT: 24 hr ambulatory ECG. Diaries kept.
TIME OF YEAR:
ANALYSIS: mean & SD. Paired T-test - awake vs sleep.
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK:
TROUGH:
RANGE: 0-1,863 PVCs/hr
MEAN: 444 ± 454 PVCs/hr
SHAPE OF WAVEFORM:
OTHER: number of PVCs was NS different waking vs sleeping. N=42, N=25, had decreased PVCs with sleep; N=17, had increased PVCs with sleep. Awake - 475 ± 477 PVCs/hr. Asleep - 439 ± 391 PVCs/hr. HR decreased from 89 ± 17 awake to 70 ± 14 asleep.
LIMITATIONS: no cosinor analysis

F. HALBERG, REINBERG, LAGOGUEY (1983)
SUBJECTS: N=3 healthy mother and 2 daughters Age: 45 yr; 13 yr; 9 yr (at start) Gender: females
VARIABLE(S): HR
METHODS: FREQUENCY: daily or several times daily
LENGTH: 3 to 5 yrs
MEASUREMENT: no details
TIME OF YEAR: 1965 to 1970
ANALYSIS: Graphic. Cosinor: single.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: circannual - 365.25 day; 24 hr
ACROPHASE: Mother - April to Dec; Daughter 1 - July (beginning); Daughter 2 - July (end)
AMPLITUDE:
MESOR:
SHAPE OF WAVEFORM: sinusoidal
OTHER: mothers acrophase shifted from year to year
LIMITATIONS: cosinor data not presented for 24 hr rhythm.

CANADA, et al (1983)
SUBJECTS: N=164 untreated ambulatory patients. (N=136, Cauc; N=26 Black; N=2 Orientals)(N=17 CHD; N=42 MI; N=23 probable CHD; N=20 hypertensives; N=8 valvular heart disease; N=14 MVP; N=40 no heart disease) Age: 57 ± 11 yr Gender: N=136 males; N=28 females
VARIABLE(S): PVCs
METHODS: FREQUENCY: continuous
LENGTH: 3 - 24 hr periods with > 30 PVCs/hr on each tape
MEASUREMENT: ECG-R taped. Diary kept. Assumed the patients slept 0000 to 0500.
TIME OF YEAR: up to 2 wk between recordings
ANALYSIS: scanner used. ANOVA. Logarithmic transformation used on mean hourly PVC frequency. Spectral analysis.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
PEAK: 1200-1600
TROUGH: 0100-0500
RANGE: 288 PVCs/hr - 519
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER: the pattern was similar for all 7 subsets and for all 3 times. N=8 had 3 consecutive 24 hr tapes. Spectral analysis revealed in N=6 a 24 hr rhythm.
LIMITATIONS: incomplete diaries on many patients; therefore sleep duration and time was not always known. No cosinor analysis.

ROSENBERG, URETZ, DENES (1983)
SUBJECTS: N=100 (N=50 patients who had increased PVCs with sleep; N=50 NLs. Age, gender, and PVC frequency-matched) Age: PT - 63.2 ± 18.7 yr; C - 64.4 ± 16.4 yr Gender: N=58 males; N= 42 females
VARIABLE(S): PVCs & HR
METHODS: FREQUENCY: continuous
LENGTH: 24 hr
MEASUREMENT: ECG-Holter (Avionics). Patients kept diaries.
TIME OF YEAR: Nov 1979 to Feb 1981
ANALYSIS: scanner used. Lown's classification of PVCs used. Ref to sleep: 2300 to 0700 determine from diaries. T-test. Chi-square.
FINDINGS: PERIOD: Yes X, No ___ (Patients only - PVCs)
LENGTH OF PERIOD: 24 hr
PEAK: PVCs increased to 143.2 ± 30.7 PVCs/hr during sleep (patients)
TROUGH: HR decreased during sleep in both groups. PVCs decreased to 45.2 ± 13.6 PVCs/hr while awake (patients).
RANGE: Patients HR - 69.4 ± 14.5 to 79.2 ± 12.2 p<.005. Control HR - 75.5 ± 15.8 to 82.6 ± 16.4 p<.005.
MEAN:
SHAPE OF WAVEFORM:
OTHER: Control group had no significant diurnal variation in PVCs. Patients had more PVCs with sleep than control (143.2 ± 30.7 vs 62.9 ± 16.3, p<.005). Patients had fewer PVCs during the day than control (45.2 ± 13.6 vs 67.7 ± 13.8, p<.05). Patients had increased sleep-related-complexity of PVCs compared to control. N=17 patients had V.T.
LIMITATIONS: no cosinor analysis

MANN, ALTMAN, RAFTERY, BANNISTER (1983)
SUBJECTS: N=6 controls - age & gender matched; N=6 with postural decreased B/P from autonomic failure Age: 40-74 yr
Gender: N=6 males; N=6 females
VARIABLE(S): HR
METHODS: FREQUENCY: continuous. Averaged at 1 hr intevals.
LENGTH: 24 hr (N=4-48 hr while on BR)
MEASUREMENT: ECG-HR taped (Medilog). Usual activities. Kept a diary. N=5 in hospital.
TIME OF YEAR:
ANALYSIS: HR-scanner used. Graphic: individual patient data shown.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr N=5
PEAK: during day
TROUGH: at night
RANGE: for each individual presented
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER: N=1 increased HR during sleep.
LIMITATIONS: no cosinor analysis. Not all HR data presented.

GOULD, HORNUNG, KIESO, CASHMAN, RAFTERY (1983)
SUBJECTS: N=13 patients with hypertension (Group 1); N=9 with hypertension (Group 2) Age: N=13, 38-59 yr (50.3 yr); N=9, 44-69 yr (55 yr) Gender: N=13, N=12 males; N=1 female; N=9 all males
VARIABLE(S): HR
METHODS: FREQUENCY: continuous. Averaged hourly.
LENGTH: 36-48 hr before and after prazosin
MEASUREMENT: ECG-HR taped (Medilog, Oxford). Outpatients. Group 2 was on beta blockers also.
TIME OF YEAR:
ANALYSIS: Graphic.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
PEAK: 0700-2000 (Group 1); 1400-1800 (Group 2)
TROUGH: 2400-0500 (Group 1); 0200-0400 (Group 2)
RANGE: 62-100 (Group 1); 57-75 (Group 2)
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER: circadian rhythm in HR occurred in both groups before and after drug.
LIMITATIONS: no cosinor analysis. Unknown when subjects slept.

DE SCALZI, et al (1984)
SUBJECTS: N=16 (N=11 NLs; N=5 with CHD), all having PACs or PVCs
Age: 59 ± 18 yr Gender:
VARIABLE(S): HR, PVCs, & PACs
METHODS: FREQUENCY: continuous
LENGTH: 96 hr
MEASUREMENT: ECG-HR taped (Holter)
TIME OF YEAR:
ANALYSIS: Cosinor: single and population
FINDINGS: PERIOD: Yes X, No ___ HR
LENGTH OF PERIOD: 24 hr
ACROPHASE: 1256 to 1736
AMPLITUDE:
MESOR:
SHAPE OF WAVEFORM:
OTHER:
LIMITATIONS: Significant circadian rhythms of PVCs for the majority of the subjects, with acrophases distributed along the 24 hours. Significant circadian rhythms in PACs for 8 subjects, with acrophases occurring between 0424 and 1812. A spectrum of significant ultradian rhythms in heart rate with various periodicities, both in normal and in CHD patients. Significant ultradian rhythms in PVCs for 8 subjects with periods ranging from 5 1/4 to 17 hr. No significant circadian group rhythm for PVCs and PACs.

SAITO, MATSUYAMA, NIKI, MORI (1984)
SUBJECTS: N=21 with VT Age: 28-86 yr Gender: N=12 males; N=9 females
VARIABLE(S): VT (3 or more PVCs in a row)
METHODS: FREQUENCY: continuous
LENGTH: 24 hr
MEASUREMENT: ECG (Avionics). Usual daily routine. Diaries kept.
TIME OF YEAR:
ANALYSIS: scanner used. Graphic. Frequency only.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
PEAK: VT increased in morning (0700-0900) and evening (1500-2100)
TROUGH: VT decreased at night (0100-0700)
RANGE: 0-73 episodes of VT
MEAN:
SHAPE OF WAVEFORM: 2 peaks, sinusoidal
OTHER: N=18 had single focus VT during day > night. N=3 had multifocal VT during night > day. VT decreased by 75% during sleep
LIMITATIONS: no cosinor analysis

DICKINSON, SCOTT (1984)
SUBJECTS: N=100 healthy subjects Age: 14-16 yr Gender: males
VARIABLE(S): R
METHODS: FREQUENCY: continuous
LENGTH: 48 hr
MEASUREMENT: ECG-HR taped (Oxford). Kept diaries. Usual activities assumed.
TIME OF YEAR:
ANALYSIS: scanner used.
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK: during day
TROUGH: sleep
RANGE: 23-95 PVCs/hr (sleep) to 45-2000 PVCs/hr (day)
MEAN:
SHAPE OF WAVEFORM:
OTHER: all had sinus arrhythmia. 3% had VT. 41% had PVCs (75% were multiformed).
LIMITATIONS: no cosinor analysis

F. HALBERG, DRAYER, CORNELISSEN, WEBER (1984)
SUBJECTS: N=40 healthy adults Age: 23-60 yr Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: 7.5 min intervals
LENGTH: 24 hr X 2 (one month apart)
MEASUREMENT: usual routines. No excessive physical activity. ECG-HR (Pressurometer III).
TIME OF YEAR: March 3 - November 7, 1983
ANALYSIS: scanner used. Cosinor: single and population (periods assessed: 24 hr; 8 hr; 6 hr; 4.8 hr; 4 hr; 3.43 hr; 1.71 hr).
FINDINGS: PERIOD: Yes X, No ___ ($p<.001$)
LENGTH OF PERIOD: 24 hr, 3.43 hr
ACROPHASE: 1400 (1336, 1428)
AMPLITUDE: 10.29 (8.87, 11.72)
MESOR: 73.9 ± 1.1
SHAPE OF WAVEFORM: sinusoidal
OTHER: amplitude decreases with age; 12.44 (21-30 yr) to 9.42 (51-60 yr). Circannual rhythm in HR - acrophase - 106° (-27°, -169°). (early April) ($p=.03$).
LIMITATIONS: all HR analysis not presented

HANSON, et al. (1984)
SUBJECTS: N=16 pairs of twins reared apart. N=1 triplets
Age: 23 to 52 yr (32.8) Gender: N=8 pairs, 1 set triplets-males; N=8 pairs-females
VARIABLE(S): HR
METHODS: FREQUENCY: continuously. Averaged at 1 hr intervals
LENGTH: 24 hr
MEASUREMENT: ECG-HR (Avionics)
TIME OF YEAR: over two years
ANALYSIS: scanner used. Cosinor: single and group.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
ACROPHASE: 1415 (0942, 1848)
AMPLITUDE: 10.97 ± 6.57
MESOR: 83.3 ± 9.45
SHAPE OF WAVEFORM: sinusoidsl
OTHER:
LIMITATIONS: none noted

KHALEQUE (1984)
SUBJECTS: N=23 shift workers; N=7 day workers Age: 28 yr
Gender: females
VARIABLE(S): HR
METHODS: FREQUENCY: 5 times during working day at 1 1/2 hr intervals.
LENGTH: 8 hr
MEASUREMENT: shift workers rotated shifts weekly. Shift - 0600-1400 (1 wk); Shift 1400-2200 (next week). Day workers 0745-1625. HR was measured with a heart beat detector where a flashing light is counted for 1 min.
TIME OF YEAR:
ANALYSIS: Graphic. ANOVA plus Tukey's test. T-test.
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK: Shift workers - 1430, Day workers - 1400
TROUGH:
RANGE:
MEAN:
SHAPE OF WAVEFORM:
OTHER: significant changes in HR among the 5 measurements. Shift workers had higher HR. Variation was different between groups. For shift workers HR decreased during the 8 hr. For day workers HR increased to 1400 and then decreased.
LIMITATIONS: no cosinor analysis. Heart rates were only measured for 8 hr.

F. HALBERG, et al. (1984)
SUBJECTS: N=1 physician with CHD on penbutolol Age: Gender:
VARIABLE(S): HR
METHODS: FREQUENCY: 1 hr intervals
LENGTH: 24 hr x 2
MEASUREMENT: self measured
TIME OF YEAR:
ANALYSIS: Graphic. Cosinor: single.
FINDINGS: PERIOD: Yes _X_, No ___ p<.003
LENGTH OF PERIOD: 24 hr
ACROPHASE: 0308
AMPLITUDE: 3
MESOR: 59
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: age and gender unknown. Small N. Unknown when subject slept.

BENOWITZ, KUYT, JACOB (1984)
SUBJECTS: N=10 healthy subjects Age: 21-63 yr (39 yr)
Gender: females
VARIABLE(S): HR
METHODS: FREQUENCY: hourly
LENGTH: 13 days
MEASUREMENT: on a research ward. 4 days of 3 treatments (own cigarettes, other cigarettes, and abstinence). ECG-HR taped (Avionics).
TIME OF YEAR:
ANALYSIS: scanner used. ANOVA.
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr all three treatments
PEAK: 0900-1900
TROUGH: 2300-0700
RANGE:
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: no cosinor analysis

MOSKIN (1984)
SUBJECTS: N=10 polar scientists Age: 25-39 yr Gender: males
VARIABLE(S): HR, CO
METHODS: FREQUENCY: measured at 0700, 1100, 1500, 1900, 2300
LENGTH: 3-6 days winter and fall x 2 at different levels of solar radiation.
MEASUREMENT: in Antartica. CO measured using Broemser-Ranke formula. Sphygmograms of carotid and femoral arteries.
TIME OF YEAR: March-April, June 1974.
ANALYSIS: descriptive statistics only.
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr (independent of the L:D cycle)
PEAK: HR - 1500 (all three times), CO - 1500 (all three times)
TROUGH: HR - 0700 (all three times), CO - 0700 (all three times
RANGE: HR=48-64 to 45-56; CO=4.5-7.5
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: no cosinor analysis. Unknown when subjects slept.

BINGHAM, CORNELISSEN, E. HALBERG, F. HALBERG (1984)
SUBJECTS: N=1, healthy subject Age: 60 yr Gender: female
VARIABLE(S): HR
METHODS: FREQUENCY: approximately 10 min intervals (Interuptions ranged from 1-31 hr). From 2400-0700 hourly.
LENGTH: 26 days
MEASUREMENT: pulse self measured using an oscillometric instrument (Nippon Colin).
TIME OF YEAR: October 24 to November 19, 1980
ANALYSIS: Graphic. Cosinor: single.
FINDINGS: PERIOD: Yes _X_, No ___ p<.01
LENGTH OF PERIOD: 24 hr
ACROPHASE: approximately 1800
AMPLITUDE:
MESOR:
SHAPE OF WAVEFORM:
OTHER: circadian rhythm documented over 26 days. Within a week there is about 35% deviation from precise 24 hr period.
LIMITATIONS: no discussion of sleep activity period. No data on 24 hr variability. Cosinor data not presented.

FARR, KEENE, SAMSON, MICHAEL (1984)
SUBJECTS: N=11 surgical patients; N=10 age/gender-matched controls Age: 22 to 42 yr (30.7 yr)
Gender: females
VARIABLE(S): HR
METHODS: FREQUENCY: 2 hr intervals x 7
LENGTH: 0800-2200 x 4 days
MEASUREMENT: all subjects were day active, in good health, and having abdominal surgery. Apical HR.
TIME OF YEAR:
ANALYSIS: Cosinor.
FINDINGS: PERIOD: Yes _X_, No ___ p<.05
LENGTH OF PERIOD: 24 hr
ACROPHASE: controls 1730; postop 2200; at home 1300
AMPLITUDE: controls 13; postop 15; at home 18
MESOR: controls 71; postop 88; at home 72
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: data not obtained during sleep.

ADAMIAN, ASLANIAN, GRIGORIAN (1984)
SUBJECTS: N=141 (N=76 CHD without prior MI; N=65 CHD with prior MI) and N=26 NLs Age: N=65 (50.8 ± 7 yr); N=26 (43.2 ± 4 yr) Gender:
VARIABLE(S): HR, CO, & SV
METHODS: FREQUENCY: 3 hr intervals
LENGTH: 24 hr
MEASUREMENT: ECG-HR & R. Slept 2230 to 0730. Standard timing of meals. CO by radiocardiography and the Starr formula.
TIME OF YEAR:
ANALYSIS: Cosinor. Ref to sleep.
FINDINGS: PERIOD: Yes _X_, No ___ p<.05 HR, CO, SV
LENGTH OF PERIOD: 24 hr
ACROPHASE: HR N=26 1834 (1319, 2014); N=76 1526 (1350, 1704); N=65 1416 (1234, 1612). CO N=26 1930 (1700, 2142); N=76 1632 (1435, 1831); N=65 1309 (1150, 1443). SV N=26 0325 (p>.05); N=76 1345 (1054, 1532); N=65 1252 (1125, 1428).
AMPLITUDE: HR N=26 2.6 (0.9, 4.4); N=76 3.1 (2.2, 3.9); N=65 2.7 (1.8, 3.6). CO N=26 .33 (0.15, 0.51); N=76 .26 (0.17, 0.36); N=65 .31 (0.23, 0.43). SV N=26 1.6; N=76 2.6 (1.8, 3.8); N=65 3.2 (2.1, 4.3).
MESOR: HR N=26 85.6 (81.3, 90.3); N=76 69.0 (66.7, 71.3); N=65 70.9 (68.1, 73.6). CO N=26 4.7 (4.2, 5.2); N=76 3.3 (3.1, 3.5); N=65 3.2 (2.9, 3.4). SV N=26 57.2; N=76 46.6 (44.0, 48.3); N=65 43.1 (40.8, 45.4).
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: gender of subjects unknown.

CARADENTE, AHLGREN, F. HALBERG (1984)
SUBJECTS: N=1 healthy subject Age: 60 yr Gender: female
VARIABLE(S): HR
METHODS: FREQUENCY: 440 observations
LENGTH:
MEASUREMENT: room restricted. Automatic monitoring of HR (Nippon Colin)
TIME OF YEAR:
ANALYSIS: Cosinor: single
FINDINGS: PERIOD: Yes _X_, No ___ p<.001
LENGTH OF PERIOD: 24 hr
ACROPHASE: 1544 (1444, 1644)
AMPLITUDE: 3.8 (2.9-4.7)
MESOR: 68.1 ± 0.3
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: only 1 subject

LOWN, CALVERT, ARMINGTON (1985)
SUBJECTS: N=13 (CVD N=10; NLs N=3). Age:
Gender: N=4 males; N=9 females
VARIABLE(S): R
METHODS: FREQUENCY: continuous
LENGTH: 2-24 hr (1 wk apart)
MEASUREMENT: ECG - HR taped. Regular routine followed. Slept at home. Kept diary.
TIME OF YEAR:
ANALYSIS: frequency only
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK:
TROUGH:
RANGE:
MEAN:
SHAPE OF WAVEFORM:
OTHER: In 61.5% - same time of maximal PVCs was found in 2-24 hr periods. In 46% - same decreased in PVCs with sleep in 2-24 hr periods. In 38.5% - no reproducibility of sleep-wake comparison. Atrial arrhythmias increased with sleep (sinus bradycardia, sinus pauses, junctional rhythm, PACs, brief SVT).
LIMITATIONS: no cosinor analysis. Age unknown.

RASMUSSEN, JENSEN, SCHNOHR, HANSEN (1985)
SUBJECTS: N=111 healthy subjects Age: 20-79 yr (median 50 yr)
Gender: N=57 males; N=54 females
VARIABLE(S): HR & PVCs
METHODS: FREQUENCY: continuous. Averaged hourly.
LENGTH: 24 hr
MEASUREMENT: ECG-HR & R taped (Hittman Comp-Act IV)
TIME OF YEAR: March-July, 1983
ANALYSIS: scanner used. Chi square test. Rank sum test. T-test.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
PEAK: PVCs - daytime (females = 1000-1600; males = 1000-2000). HR 0800-1800.
TROUGH: PVCs & HR nighttime
RANGE: HR 61 ± 19 (2 SD) to 98 ± 34 (2 SD)
MEAN: 70 ± 28 (2 SD)
SHAPE OF WAVEFORM: sinusoidal
OTHER: 61% had PVCs. PVCs increased with age.
LIMITATIONS: no cosinor analysis. Unclear when subjects slept.

DE LEONARDIS, DE SCALZI, FABIANO, CINELLI (1985)
SUBJECTS: N=49 (N=21 healthy subjects; N=28 risk for CHD) Age: 32-48 yr; (42 yr) Gender: males
VARIABLE(S): HR & R
METHODS: FREQUENCY: continuous
LENGTH: 4 days
MEASUREMENT: hospitalized. Not confined to bed. Followed hospital routine. ECG-HR (Avionics). Slept 2300-0700.
TIME OF YEAR:
ANALYSIS: Graphic. Cosinor: individual and group. Ref to sleep. Linear regression.
FINDINGS: PERIOD: Yes X, No ___ $p<.05$ individuals
LENGTH OF PERIOD: circadian and ultradian (4 hr 12 min to 20 hr PACs)(5 hr 12 min to 17 hr PVCs) in PACs and PVCs and HR.
ACROPHASE: HR 1301-1827 group - 1529. PACs 0424-1912. PVCs 0900-2352. Cosinor analysis of PACs and PVCs for group - NS.
AMPLITUDE: NL 9.49 (8.52, 10.45). Risk 7.767 to 11.12.
MESOR: NL = 73 ± 2.9. Risk = 73 ± 2.9 to 80 ± 2.1.
SHAPE OF WAVEFORM: sinusoidal
OTHER: inverse correlation between amplitude of HR circadian rhythm and age ($r=-.885$ $p<.001$)
LIMITATIONS: none noted

STEFIKOVA, SOVCIKOVA, BRONIS (1985)
SUBJECTS: N=24 healthy students Age: 22 yr Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: 2 hr intervals during day; 3 hr intervals at night
LENGTH: 61 hr
MEASUREMENT: ECG-HR
TIME OF YEAR:
ANALYSIS: Cosinor: single.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
ACROPHASE: PM
AMPLITUDE:
MESOR:
SHAPE OF WAVEFORM:
OTHER: much individual variation
LIMITATIONS: unknown when subjects slept. 24 hr data not provided. Cosinor analysis not presented in abstract.

BREVETTI, CHIARELLO, BONADUCE, CANONICO, BREGLIO, CONDORELLI (1985)
SUBJECTS: N=2, orthostatic decreased B/P due to autonomic dysfunction Age: 63 and 66 yr Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: 60 min interval
LENGTH: 1-24 hr period without propranolol; 1-24 hr period after 3 weeks of propranolol.
MEASUREMENT: ECG-HR chest lead. In hospital.
TIME OF YEAR:
ANALYSIS: Graphic.
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK: Subj. #1 - before drug 1530-1730; after drug 1300. Subj. #2 - before drug 1500; after drug 1600.
TROUGH: Subj. #1 - before drug 0300; after drug 2100. Subj. #2 - before drug 0530; after drug 0630.
RANGE: Subj. #1 before drug 70-88; after drug 64-81. Subj. #2 - before drug 62-92; after drug 62-82.
MEAN:
SHAPE OF WAVEFORM: flat, two peaks during day
OTHER:
LIMITATIONS: no cosinor analysis

KARJALAINEN & VIITASALO (1986)
SUBJECTS: N=27 with febrile infections (URI) Age: 18-29 yr (median 20 yr) Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: continuous
LENGTH: 24 hr x 2 (1st on admission; 2nd recovery)
MEASUREMENT: in hospital. ECG-HR taped (Avionics).
TIME OF YEAR:
ANALYSIS: scanner used. T-test. Fisher's exact test.
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr
PEAK: daytime (1800-1900)
TROUGH: night (0400)
RANGE: 1st 68-103. 2nd 51-77.
MEAN: 1st 84. 2nd 66.5
SHAPE OF WAVEFORM: sinusoidal
OTHER: attenuation of amplitude during fever.
LIMITATIONS: no cosinor analysis

GROSGOGEAT, et al. (1986)
SUBJECTS: N=134 NLs Age: 42.5 ± 14 yr Gender: N=59 males; N=75 females
VARIABLE(S): HR & R
METHODS: FREQUENCY: continuous and averaged at 1 hr intervals
LENGTH: 24 hr
MEASUREMENT: ECG-HR taped (Holter)
TIME OF YEAR:
ANALYSIS:
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr
PEAK: during day
TROUGH: 2400-0600
RANGE: 64 ± 8 (night) to 82 ± 10 (day)
MEAN: 75 ± 9
SHAPE OF WAVEFORM: sinusoidal
OTHER: 22% had no ectopics. Supraventricular extrasystoles in 68% during day and in 50% during night. PVCs in 42% during day and in 23% at night.
LIMITATIONS: no cosinor analysis

CAFIERO, SCALZONE, BORGIA, COSTANTINO, FIORENZA, ERAMO (1986)
SUBJECTS: N=34 (N=17 cardiac patients; and N=17 NLs). All had >30 PVC/hr. Age: patients 56 ± 14 yr; NLs 41 ± 18 yr Gender: patients: N= 13 male; N=4 female. NLs: N=10 males; N=7 females.
VARIABLE(S): PVCs
METHODS: FREQUENCY: continuous
LENGTH: 24 hr
MEASUREMENT: ECG-HR taped (Avionics)
TIME OF YEAR:
ANALYSIS: Cosinor: single and group
FINDINGS: PERIOD: Yes _X_, No ___ $p<.05$ N=11 patients and N=13 NLs.
LENGTH OF PERIOD: 24 hr
ACROPHASE: 1500-1800
AMPLITUDE: much individual difference
MESOR: patients=228.1 ± 75.4 PVCs/hr; NLs=266.6 ± 51 PVCs/hr
SHAPE OF WAVEFORM:
OTHER: group cosinor analysis - NS
LIMITATIONS: unknown when subjects slept

FAVRE, ADAMEC, BOXHO (1986)
SUBJECTS: N=11 ambulant hypertensive patients Age: 20-60 yr
Gender: N=10 males; N=1 female
VARIABLE(S): HR
METHODS: FREQUENCY: 15 min. Averaged hourly.
LENGTH: 24 hr x 3 (placebo, 4 wk of bopindolol, and 8 wk of bopindolol)
MEASUREMENT: ECG-HR taped (Pressurometer II). Normal activity.
TIME OF YEAR:
ANALYSIS: Wilcoxon signed rank test
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr (all 3 times)
PEAK: 0900-2100
TROUGH: night
RANGE: 12 ± 9 ($p<.0001$)
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER: mean HR decreased 7 ± 8 to 8 ± 5 ($p<.01$) with bopindolol
LIMITATIONS: unknown when subjects slept. No cosinor analysis.

GUAGNANO, et al. (1986)
SUBJECTS: N=15 healthy males (N=7 young; N=8 elderly)
Age: N=7, 26 ± 1 yr (25-29 yr); N=8, 72 ± 3 yr (64-78 yr) Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: 4 hr intervals
LENGTH: 24 hr
MEASUREMENT: dark 2300-0700; same diet - 3 meals given at equal intervals.
TIME OF YEAR:
ANALYSIS: Cosinor.
FINDINGS: PERIOD: Yes _X_, No ___ $p<.05$
LENGTH OF PERIOD: 24 hr
ACROPHASE: young N=4:1920 (1423, 0110); old N=6:1407 (1131-2126)
AMPLITUDE: young 5.20 ± 1.57; old 4.41 ± 0.59
MESOR: young 69.71 ± 4.55; old 71.59 ± 6.39
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: small N

LANZA, LUCENTE, REBUZZI, SPAGNOLO, DULCIMASCOLO, MANZOLI (1986)
SUBJECTS: N=7 patients with ventricular parasystole
Age: 12-75 yr (50.6 yr) Gender: N=6 males; N=1 female
VARIABLE(S): HR & R
METHODS: FREQUENCY: continuous. Averaged hourly.
LENGTH: 24 hr
MEASUREMENT: ECG-HR & R taped (Holter). Similar schedule. Slept 2230-0700.
TIME OF YEAR:
ANALYSIS: scanner used. Cosinor: single and group.
FINDINGS: PERIOD: Yes _X_, No ___ $p<.05$
LENGTH OF PERIOD: 24 hr
ACROPHASE: HR - 1327; Parasystole - 1342
AMPLITUDE: HR - 9.53; Parasystole - 3.64 beats/min
MESOR: HR - 73.28; Parasystole - 38.31 beats/min
SHAPE OF WAVEFORM: sinusoidal
OTHER: N=5 had continuous parasystole.
LIMITATIONS: small N

WEBER (1986)
SUBJECTS: N=197 patients with CHD; N=89 patients with cardiomyopathy; N=1688 patients with CVD
Age: N=197, 27-80 yr (57 ± 10 yr); N=89, 20-70 yr (52 ± 11 yr); N=1688, 3-88 yr (50 ± 18 yr) Gender: N=197, N=172 males; N=25 females. N=89, N=68 males; N=21 females
VARIABLE(S): HR
METHODS: FREQUENCY: continuous
LENGTH: 24 hr
MEASUREMENT: ECG-HR taped
TIME OF YEAR:
ANALYSIS: scanner used. Correlation. Linear and multiple regression. Chi square.
FINDINGS: PERIOD: Yes _X_, No ___ PVCs in 60% of CHD and in 84% of cardiomyopathy
LENGTH OF PERIOD: 24 hr
PEAK: day
TROUGH: night
RANGE:
MEAN:
SHAPE OF WAVEFORM:
OTHER: with decreased LV function, there is increased HR and a loss of circadian periodicity. PVCs increase from 39 to 53% (CHD) with decreasing LV function.
LIMITATIONS: no cosinor analysis

TAMMARO, et al. (1986) continued
SUBJECTS: N= Age: Gender:
VARIABLE(S): PVCs
METHODS: FREQUENCY:
LENGTH:
MEASUREMENT:
TIME OF YEAR:
ANALYSIS: Cosinor: individual, group. ANOVA
FINDINGS: PERIOD: Yes _X_, No ___ p<.04 (individual analysis, not group)
LENGTH OF PERIOD: 24 hr in 43.3% of the healthy and 58.6% of the patients
ACROPHASE: see below
AMPLITUDE: see below
MESOR: see below
SHAPE OF WAVEFORM: healthy subjects had 5 peaks during day; heart patients had 3 peaks during the day.
OTHER: N=30, 72.4% had less than 100 PVCs in 24 hr; 10.3% had 101-200 PVCs in 24 hr; 12.2% had greater than 200 PVCs in 24 hr. N=42, 6.7% had PVCs; N=29, 6.9% had less than 30 PVCs per hr; 75.9% had 31-200 PVCs per hr; 17.2% had greater than 201 PVCs per hr. PVCs occurred significantly more often during the day for all 5 subjects. In healthy subjects, there was an abrupt increase at 0600. In heart patients with 30-150 PVCs per hr, 17 subjects had significant circadian rhythm (Mesor 69.92 ± 38.88; Amplitude 28.40 ± 35.18; Acrophase 1404 (1020, 2016). 36.7% of the healthy subjects and 31.19% of the heart patients had nocturnal acrophases. Much individual difference.
LIMITATIONS: none noted

TIMBAL, COLIN, MAROTTE (1986)
SUBJECTS: N=6 NLs Age: 19-21 yr Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: 3 hr intervals
LENGTH: 24 hr
MEASUREMENT: resting supine for 24 hr. Fed at 0800, 1330, 1930.
TIME OF YEAR:
ANALYSIS: variance analysis - 2 harmonics of 24 hr.
FINDINGS: PERIOD: Yes _X_, No ___ p<.05
LENGTH OF PERIOD: 24 hr
ACROPHASE: 1437 ± 530 min
AMPLITUDE: 4.6 ± 4
MESOR: 56.8 ± 4.6
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: small N. Only 1 24-hr period at 3 hr intervals.

NORTHCOTE, MACFARLANE, KESSON, BALLANTYLE (1986)
SUBJECTS: N=10 thyrotoxic subjects Age: 20-66 yr (41 ± 14.4 yr)
Gender:
VARIABLE(S): HR, PVCs, & PACs
METHODS: FREQUENCY: continuous and averaged at 1 hr intervals
LENGTH: 24 hr before and after treatment (3 mo later)
MEASUREMENT: ECG-HR & R taped (Oxford). Normal outpatient activities. Avoided coffee, tea, and tobacco.
TIME OF YEAR:
ANALYSIS: scanner used. T-test.
FINDINGS: PERIOD: Yes _X_, No ___ HR p<.01
LENGTH OF PERIOD: 24 hr
PEAK: 0800-1400
TROUGH: 0000-0600
RANGE: Before - 84.3 ± 6.54 to 126.1 ± 16.99. After - 66.6 ± 9.14 to 100.9 ± 6.67.
MEAN: Before - 104 ± 10.8. After - 82 ± 6.8.
SHAPE OF WAVEFORM: sinusoidal HR
OTHER: All had PACs and PACs increased in the middle third of the day (p<.01) after treatment . PVCs increased 0530 to 2100 and decreased with sleep. VT - N=2 (0500-0830).
LIMITATIONS: no cosinor analysis. Gender unknown.

REEVES, SHAPIRO, THOMPSON, JOHNSEN (1986)
SUBJECTS: N=15 control; N=23 transplant; N=46 heart transplant recipients; N=30 increased B/P; N=10 diabetics
Age: 41-51 yr Gender: N=23 (N=22 male; N=1 female); N=15 (N=9 males; N=6 females)
VARIABLE(S): HR
METHODS: FREQUENCY: continuously
LENGTH: 24 hr
MEASUREMENT: ECG-HR taped (Avionics). Diaries were kept. Mostly in hospital.
TIME OF YEAR: 1980-1984
ANALYSIS: scanner used. Graphic.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
PEAK: during day
TROUGH: during night
RANGE:
MEAN:
SHAPE OF WAVEFORM:
OTHER: Day N=46 93.4 ± 1.8; N=30 76.5 ± 2.1; N=10 94.7 ± 3.3. Night N=46 85.8 ± 1.9; N=30 65.3 ± 1.8; N=10 86.2 ± 4.6. Change N=46 -7.9 ± 1.3%; N=30 -14.5 ± 1.4%; N=10 -9.6 ± 3%. N=15 decreased HR with sleep (16 ± 2.1%). N=23 decreased HR with sleep (8 ± 1.6%).
LIMITATIONS: no cosinor analysis. Sleep pattern unknown. Only mean for day and night presented.

MIR (1986)
SUBJECTS: N=28 stable patients with arrhythmias Age: 20 to 70 yr (48 ± 15) Gender: N=17 males; N=11 females
VARIABLE(S): R
METHODS: FREQUENCY: continuous
LENGTH: 1 week
MEASUREMENT: ECG-HR (Avionics). Diary kept.
TIME OF YEAR:
ANALYSIS: paried T-test between each 4 hr period with the 4 hr sleep period (2400-0400).
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK: 1600 to 2400 (p<.001). Increased VT 1200 to 2400
TROUGH: 0400 to 1200 (p<.001). Decreased VT 0400 to 0800.
RANGE:
MEAN:
SHAPE OF WAVEFORM:
OTHER: higher frequency of PVCs during midday to midnight (p<.05) (especially 2000-2400). Higher frequency of SVT between 1200 to 2000 than during 0000 to 0800 (p<.05).
LIMITATIONS: no cosinor analysis

ROSSI, SFORZA, CARANDENTE (1986)
SUBJECTS: N=18 relatively healthy subjects Age: 90-98 yr (92.3 ± 2.3 yr) Gender: N=7 males; N=11 females
VARIABLE(S): HR, PACs, & PVCs
METHODS: FREQUENCY: continuous. Averaged at 1 hr intervals.
LENGTH: 24 hr
MEASUREMENT: in a rest home. Slept 2200-0600. Ate meals at 0700, 1200, 1900. ECG-HR taped (Avionics).
TIME OF YEAR:
ANALYSIS: ECG analysis manual. Graphic. Cosinor: single and population.
FINDINGS: PERIOD: Yes X, No ___ p<.0001 (population)
LENGTH OF PERIOD: 24 hr - HR. N=14 had significant rhythms using single cosinor analysis.
ACROPHASE: 1600 (1300, 1830)
AMPLITUDE: 5.58 (1.37, 9.83)
MESOR: 79.26 ± 2.56
SHAPE OF WAVEFORM: sinusoidal
OTHER: all had PACs - sinusoidal rhythm with peak in the late morning and afternoon. N=1 had atrial fibrillation. N=3 had < 100 PACs/24 hrs. N=9 had a significant circadian rhythm in PACs with acrophase between 0060 and 2152, mesor 5.3 to 192.5/min and amplitude 5.8 to 193.3/min. Population did not have a significant circadian rhythm in PACs or PVCs. N=12 (66%) had PVCs < 100/24 hr. N=5 (out of 15) had a significant circadian rhythm in PVCs with acrophases between 0080 to 2300, mesors 0.4 - 648.1/min and amplitude 0.3 to 217.2/min.
LIMITATIONS: none noted

KANTELIP, SAGE, DUCHENE-MARULLAZ (1986)
SUBJECTS: N=50 without CVD sedentary Age: 80-100 yr (86 ± 6 yr) Gender: N=6 males; N=44 females
VARIABLE(S): HR & R
METHODS: FREQUENCY: continuous - averaged very 10 min
LENGTH: 24 hr
MEASUREMENT: no medications. ECG taped (Medilog 1).
TIME OF YEAR: over a 2 yr period
ANALYSIS: Graphic. Frequency
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr - HR
PEAK: 2-5 PM
TROUGH: 4-6 AM
RANGE: 64 ± 1 to 78 ± 3 (43 to 180)
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER: SVT in 28%. SV ectopics in all cases <1/hr in 25%. PVCs <9 50%; >20/hr in 65%. >10-50/hr in 32%. Pairs in 8%. 1 or more in 98%. Multifocal in 18%. VT in 2%. Sleeping rates <50 in 14%. Pauses 1.8-2 seconds in 12% (sinus arrhythmia).
LIMITATIONS: no cosinor analysis

ORTH-GOMER, HOGSTEDT, BODIN, SODERHOLM (1986)
SUBJECTS: N=147, actively employed, healthy subjects Age: 15-66 yr (44 ± 14.1 yr) Gender: males
VARIABLE(S): HR & PVCs
METHODS: FREQUENCY: continuous
LENGTH: 24 hr
MEASUREMENT: ECG-HR (Holter) during regular activity.
TIME OF YEAR:
ANALYSIS: ANOVA: medians and logs used. Frequency and descriptive statistics. Skewed distribution. Chi square test.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
PEAK: PVCs increased between 1100-1330. HR increased during day (work) peak at 1300.
TROUGH: lower number of PVCs during sleep. HR lowest 2300-0500.
RANGE: HR 60-88
MEAN:
SHAPE OF WAVEFORM: 1 peak sinusoidal - HR
OTHER: 95% had <2.9 PVCs/hr (aged 15-39 yr). 95% had <36 PVCs/hr (aged 40 and older).
LIMITATIONS: no cosinor analysis

TAMMARO, CASALE, DE NICOLA (1986)
SUBJECTS: N=30 aged with no heart disease and N=42 young adults; N=29 aged with heart disease Age: N=30 65-87 yr (73.5 ± 1.4); N=42 20-49 yr (32.1 ± 2.6); N=29 65-86 yr (74.4 ± 1.3) Gender: N=30, N=5 males; N=25 females. N=42, N=21 males; N=21 females. N=29, N=12 males, N=17 females.
VARIABLE(S): HR
METHODS: FREQUENCY: continuous
LENGTH: 24 hr
MEASUREMENT: ECG-HR taped
TIME OF YEAR:
ANALYSIS: Cosinor: group. T2 Hotelling test.
FINDINGS: PERIOD: Yes X, No ___ p<.001
LENGTH OF PERIOD: 24 hr
ACROPHASE: N=30, 1411 (1308, 1508); N=42, 1500 (1408-1500); N=29 1420 (1328, 1520).
AMPLITUDE: N=30, 8.78 ± 3.96; N=42, 12.39 ± 4.91; N=29, 8.78 ± 3.96
MESOR: N=30, 70.82 ± 8.58; N=42, 73.16 ± 4.52; N=29, 74.93 ± 11.1.
SHAPE OF WAVEFORM: sinusoidal
OTHER: Aged had a nonsignificant decrease in amplitude. Double amplitude in young was 40% of mesor and 25% in aged. During waking (0700-0900) an abrupt increase in HR.
LIMITATIONS: unknown when subjects slept.

MANCIA, et al. (1986)
SUBJECTS: N=89 (N=22 NLs; N=26 mild increased B/P; N=41 severe increased B/P Age: younger subjects 30 ± 1 yr; older subjects 54 ± 1 yr Gender: N=55 males; N=34 females
VARIABLE(S): HR
METHODS: FREQUENCY: continuous. 30 min averages.
LENGTH: 24 hr
MEASUREMENT: standardized living conditions in hospital. No medications. Night rest of similar length. ECG-HR.
TIME OF YEAR:
ANALYSIS: SD and variation coefficients (SD as a % of mean)
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK: 1230
TROUGH: 0400 (2300-0500)
RANGE: 67-88
MEAN: 75 ± 2 (NLs); 77 ± 2 (mild increased B/P); 79 ± 1 (severe increased B/P)
SHAPE OF WAVEFORM: sinusoidal
OTHER: reduction of HR with sleep. HR decreased with age. Concluded that sleep decreased HR, not a circadian effect.
LIMITATIONS: no cosinor analysis

CINCA, MOYA, FIGUERAS, ROMA, RIUS (1986)
SUBJECTS: N=12 patients who had EPS at bedside Age: 17-59 yr (40.2 yr) Gender: N=9 males; N=3 females
VARIABLE(S): HR
METHODS: FREQUENCY: 1 hr intervals
LENGTH: 24 hr
MEASUREMENT: EPS equipment
TIME OF YEAR:
ANALYSIS: ANOVA: 2 way. Coefficients of variation = SD/X x 100. Paired T-test.
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr
PEAK: 1330 - HR. AV node and myocardial refractoriness 0000-0700.
TROUGH: 0000-0700 (p<.0005) HR
RANGE:
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: no cosinor analysis

RICHARDS, NICHOLLS, ESPINER, IKRAM, CULLEN, HINTON (1986)
SUBJECTS: N=17 (N=12 with increased B/P) Age: NL=27-56 yr (40 yr) Gender: NLs - N=2 males; N=3 females
VARIABLE(S): HR
METHODS: FREQUENCY: continuously. Averaged every 5 min.
LENGTH: 24 hr
MEASUREMENT: No medications. No cigarette smoking. No caffeine. 0830-2100 day active. 2100-0900 slept. ECG-HR taped (Oxford Medical Systems).
TIME OF YEAR:
ANALYSIS: Graphic.
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr
PEAK: 1400-1600
TROUGH: 2200-0800
RANGE: 58 ± 2 to 90 ± 4
MEAN: 80 ± 6
SHAPE OF WAVEFORM: sinusoidal
OTHER: hypertensives and NLs had a similar circadian pattern.
LIMITATIONS: no cosinor analysis. Demographics about hypertensives not provided.

CINCA, MOYA, BARDIJI, FIGUERAS, RIUS (1987)
SUBJECTS: N=13 patients with left-sided Kent Bundles. Age: 16-57 yr, (35 yr). Gender: N=10 males; N=3 females
VARIABLE(S): HR
METHODS: FREQUENCY: 1-2 hr. LENGTH: 22 hr
MEASUREMENT: slept all night. 8 to 11 EPS done. No CV drugs. Meals at 1500, 1900, 0700
TIME OF YEAR:
ANALYSIS: Chi square for trend. ANOVA.
FINDINGS: PERIOD: Yes _X_, No ___ p<.005
LENGTH OF PERIOD: 24 hr
PEAK: 1300-1400
TROUGH: 0000-0300
0700-1000
RANGE:
MESOR:
SHAPE OF WAVEFORM:
OTHER: nocturnal protection against electrical induction of reciprocating tachycardia (increased refractoriness of atria, AV node, Kent Bundle, and right ventricle)
LIMITATIONS: no cosinor analysis

CINCA, MOYA, BARDIJI, FIGUERAS, RIUS (1987)
SUBJECTS: N=13 patients with left-sided Kent Bundles Age: 16-57 yr (35 yr) Gender: N=10 males; N=3 females
VARIABLE(S): HR
METHODS: FREQUENCY: 1-2 hr
LENGTH: 22 hr
MEASUREMENT: slept all night. 8 to 11 EPS done. No CV drugs. Meals at 1500, 1900, 0700.
TIME OF YEAR:
ANALYSIS: Chi square for trend. ANOVA.
FINDINGS: PERIOD: Yes X, No ___ p<.005 (HR)
LENGTH OF PERIOD: 24 hr
PEAK: 1300-1400
TROUGH: 0000-0300; 0700-1000
RANGE:
MEAN:
SHAPE OF WAVEFORM:
OTHER: nocturnal protection against electrical induction of reciprocating tachycardia (increased refractoriness of atria, AV node, Kent Bundle, and right ventricle)
LIMITATIONS: no cosinor analysis

KASTING, ECKBERG, FRITSCH, BIRKETT (1987)
SUBJECTS: N=11 healthy Age: 33-43 yr Gender: N=7 males; N=4 females
VARIABLE(S): HR
METHODS: FREQUENCY: 3 hr intervals (mean of 4 min)
LENGTH: 24 hr
MEASUREMENT: usual sleep/wake cycles in a laboratory. Read and watched T.V. Were awakened for 3 30-min periods during night. No smoking. ECG-HR.
TIME OF YEAR:
ANALYSIS: multivariate repeated measures. Correlation.
FINDINGS: PERIOD: Yes X, No ___ (p<.05)
LENGTH OF PERIOD: 24 hr
PEAK: 6-12 hr after awakening
TROUGH: 18-24 hr after awakening
RANGE:
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: no cosinor analysis

LOEBER, GOLDBERG, DONNERSTEIN, BUTLER (1987)
SUBJECTS: N=12 health students Age: 18-30 yr (24 yr) Gender:
VARIABLE(S): CO, SV, & HR
METHODS: FREQUENCY: 6 measures
LENGTH: 6 weeks
MEASUREMENT: CO (Doppler Echo) 1) random evening; 2) after overnight fast; 3) after a small breakfast with >500 ml fluid; 4) 60 min after large lunch with >1000 ml fluid; 5) 45 min after exercise; 6) random evening - 2 weeks after start. Caffeine-free liquids.
TIME OF YEAR:
ANALYSIS: individual values and mean values presented for CI and SI.
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK:
TROUGH:
RANGE:
MEAN: CI 3.7 ± 474. SI 51 ± 6.8.
SHAPE OF WAVEFORM:
OTHER: CI increased after meals and was due to increased HR. CI 1) random evening 3.590 ± 0.857; 2) before breakfast 3.409 ± 0.841; 3) after breakfast 3.810 ± 0.799; 4) after lunch 3.657 ± 0.768; 5) after exercise 4.019 ± 0.908; 6) random evening 3.694 ± 0.952. SVI 1) random evening 50.3 ± 12.4; 2) before breakfast 51.0 ± 11.4; 3) after breakfast 53.9 ± 13.0; 4) after lunch 47.0 ± 10.0; 5) after exercise 50.6 ± 12.8; 6) random evening 50.8 ± 12.8.
LIMITATIONS: no cosinor analysis. Not related to sleep/wake cycle. Gender unknown.

BERNARDI, et al. (1987)
SUBJECTS: N=7 health controls; N=7 cirrhotic patients without ascites; N=9 cirrhotic patients with ascites
Age: 24-71 yr (median 52 yr) Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: 4 hr
LENGTH: 24 hr
MEASUREMENT: same diet for 6 days. Quiet, warm room. Supine throughout study. Meals at 0900, 1230, 0630.
TIME OF YEAR:
ANALYSIS: Cosinor: single and group. Wilcoxon's rank sum test, Wilcoxon's matched-pairs. Signed-ranks test. Kolmogorov-Smirnof test. Correlations.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
ACROPHASE: controls 1208 (1020, 1401); N=7 1730 (1308, 2300); N=9 2235 (1743, 0148)
AMPLITUDE: controls 4.8 ± 0.9; N=7 3.2 ± 0.8; N=9 4.9 ± 0.8.
MESOR: controls 63.8 ± 2.9; N=7 69.8 ± 3.3; N=9 76.0 ± 4.4.
SHAPE OF WAVEFORM: sinusoidal
OTHER: with increased disease acrophases shifted towards night.
LIMITATIONS: unknown when subjects slept.

CUGINI, et al. (1987)
SUBJECTS: N=10 patients in shock in an ER Age: 20-78 yr
Gender: N=9 males; N=1 female
VARIABLE(S): HR
METHODS: FREQUENCY: continuous
LENGTH: 15-24 hr
MEASUREMENT: constant light. HR (Pressurometer Omega)
TIME OF YEAR:
ANALYSIS: Cosinor: single
FINDINGS: PERIOD: Yes X, No ___ N=7
LENGTH OF PERIOD: 24 hr
ACROPHASE: 0853, 1729, 1755, 2246, 0041, 0130, 0450
AMPLITUDE: 3-60
MESOR: 86-135
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: level of consciousness was unknown. Unknown whether subjects were day active prior to study.

MEHTA, WALSH, GOLDBERG, TOPHAM (1987)
SUBJECTS: N=20 untreated hypertensives Age: 45.3 ± 8.6 yr
Gender: N=7 males; N=13 females
VARIABLE(S): HR
METHODS: FREQUENCY: continuous and averaged at 5 min intervals
LENGTH: 24 hr
MEASUREMENT: ECG-HR (Medilog). Patients kept diaries and assumed usual activities.
TIME OF YEAR:
ANALYSIS: means
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
PEAK: day
TROUGH: night
RANGE: 22 ± 7
MEAN: day 73 ± 12; night 96 ± 11
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: no cosinor analysis

NADEMANEE, INTARACHOT, JOSEPHSON, SINGH (1987)
SUBJECTS: N=77 patients with angina Age: 61 yr
Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: continuous
LENGTH: 24 hr - 48 hr
MEASUREMENT: ECG-HR taped (Holter)
TIME OF YEAR: March 1982 to December 1986
ANALYSIS: Cosinor. Chi square test. Scanner used.
FINDINGS: PERIOD: Yes X, No ___ p<.0004
LENGTH OF PERIOD: 24 hr
ACROPHASE: 1500-1700
AMPLITUDE: 9
MESOR: 74-85
SHAPE OF WAVEFORM: sinusoidal
OTHER: trough 0300-0500
LIMITATIONS: no information about patient activity/rest schedule.

CHANNER, PAPOUCHADO, JAMES, PITCHER, REES (1987)
SUBJECTS: N=14 patients with atrial fibrillation taking digoxin
Age: 52-74 yr (59.6 yr) Gender: N=3 males; N=11 females
VARIABLE(S): HR
METHODS: FREQUENCY: continuous. Hourly max and min used.
LENGTH: 24 hr x 3. Digoxin increased and verapamil added between times. 1 month between times.
MEASUREMENT: ECG-HR taped (Medilog)
TIME OF YEAR:
ANALYSIS: ECG analyzed using a Reynolds Pathfinder II. Graphic. Descriptic statistics. Area under curve calculated.
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr
PEAK: 0800-1600
TROUGH: 0200-0600
RANGE: 75-142 (Time-1); 62-115 (Time-2); 65-118 (Time-3)
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: no cosinor analysis

CUGINI, LUCIA, LETIZIA, MURANO, SCAVO (1987)
SUBJECTS: N=23 (N=13 young; N=10 old) healthy subjects
Age: young 17-26 yr; old 70-80 yr Gender: N=15 males; N=8 females
VARIABLE(S): HR
METHODS: FREQUENCY: 15-30 min
LENGTH: 24 hr x 2: 1st CBR; 2nd inactivity 2300-0700.
MEASUREMENT: meals 0830, 1200, 1830 hospital. HR-taped (Omega). Lights on 0700; off at 2300.
TIME OF YEAR: winter, 1984, Rome, Italy
ANALYSIS: Cosinor: single and mean. Hotelling's T2 Test (multivariate analysis for vectoral units). Graphic: Chronograms.
FINDINGS: PERIOD: Yes _X_, No ___ p<.02
LENGTH OF PERIOD: 24 hr
ACROPHASE: 1st young 1556 (1252, 1848); old 1508 (1134, 1752). 2nd young 0923 (0751, 1236); old 1555 (1308, 1835)
AMPLITUDE: 1st young 3.71 (0.39, 7.03); old 3.25 (0.54, 5.96). 2nd young 5.95 (2.9-9); old 5.19 (1.41, 8.97).
MESOR: 1st young 64.70 ± 2.28; old 63.63 ± 2.08. 2nd young 66.41 ± 3.11; old 74.28 ± 2.43.
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: none noted

HORII, et al. (1987)
SUBJECTS: N=14 alpinist; N=10 healthy (all were Japanese)
Age: N=14, 26-45 yr (34.2 yr); N=10 similar to N=14
Gender: N=14, N=9 males; N=5 females. N=10, N=7 males, N=3 females.
VARIABLE(S): HR
METHODS: FREQUENCY: continuous
LENGTH: 24 hr at sea level; 16-24 hr at high altitude
MEASUREMENT: ECG-HR taped (Holter). Diaries kept and activities were not limited. No medications.
TIME OF YEAR: 1983-1984
ANALYSIS: descriptive statistics for day (awake) and night (asleep)
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr in several alpinist and in healthy subjects.
PEAK: while awake
TROUGH: while asleep
RANGE: N=10 awake 85 ± 2, asleep 61 ± 1.3. N=14 awake 76.3 ± 2.1 (sea level), 94 ± 4.9 (high altitude), asleep 61.6 ± 2.1 (sea level), 74.6 ± 6.7 (high altitude).
MEAN:
SHAPE OF WAVEFORM:
OTHER:
LIMITATIONS: in several alpinist the circadian rhythm of HR disappeared at high altitude. No cosinor analysis.

CARPEGGIANI, et al. (1987)
SUBJECTS: N=11 patients with variant angina in a CCU
Age: 38-68 yr (51 ± 9 yr) Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: continuous. Averaged hourly.
LENGTH: 4-13 days
MEASUREMENT: ECG-HR taped (Holter). No medications. CCU routine. Rested between 2200-0630.
TIME OF YEAR:
ANALYSIS: harmonic regression
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr
PEAK: day
TROUGH: 2232-0502
RANGE:
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER: 87% of the 70 days (61 days) had a significant circadian rhythm. 64% of the patients (N=7) consistently maintained a circadian rhythm in HR.
LIMITATIONS: no cosinor analysis

SENSI, CAPAN, ANGELUCCI, GUAGNANO (1987)
SUBJECTS: N=12 healthy subjects (N=6 young; N=6 old)
Age: young 27 ± .8 yr; old 75 ± 2 yr Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: 4 hr
LENGTH: 24 hr
MEASUREMENT: 3 days before and during study, rest and darkness 2300-0700. Same diet - 3 isocaloric meals given at equal intervals.
TIME OF YEAR:
ANALYSIS: Cosinor
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
ACROPHASE: young 1920 (1423-0110); old 1407 (1131, 2126)
AMPLITUDE: young 5.20 ± 1.57; old 4.41 ± 0.59
MESOR: young 69.71 ± 4.55; old 71.59 ± 6.39
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: none noted

TURJANMAA, KALLI, MAJAHALME, SARANUMMI, UUSITALO (1987)
SUBJECTS: N=14 normals Age: 22-50 yr (34 ± 7.2 yr) Gender:
VARIABLE(S): HR
METHODS: FREQUENCY:
LENGTH: 30 hr
MEASUREMENT: ECG-HR taped (Oxford Medilog). Ambulatory conditions. Slept at home. Worked in the daytime. The last 22.5-23.5 hr data used for analysis.
TIME OF YEAR:
ANALYSIS: Graphic. Computer analyzed data. Time series curves using 1 hr, 5 hr, & 24 hr periods. T-tests.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
PEAK: day
TROUGH: night
RANGE: 60 ± 8 to 85 ± 10
MEAN: 76 ± 7.9
SHAPE OF WAVEFORM: sinusoidal
OTHER: sleep/wake cycle and activity affect variability.
LIMITATIONS: no cosinor analysis

SCARPELLI, et al. (1987)
SUBJECTS: N=3 patients with hypertension with and without treatment Age: 20-31 yr Gender: N=2 males; N=1 unknown
VARIABLE(S): HR
METHODS: FREQUENCY: automatic - every 1 hr and self measured (0800, 1200, 1600, 2000, 0000). Subject #1 - 3 time spans: 2 days, 20 days, and 16 days. Subject #2 - 2 time spans: 7 days, 11 days. Subject #3 - 5 time spans: 10 days, 25 days, 19 days, 33 days, 19 days.
LENGTH: variable (2-33 days)
MEASUREMENT: HR (Nippon Colin)
TIME OF YEAR: Subj #1 Jan 18-19, 1985; Jan 24-Feb 12, 1985; Sept 11-26, 1986. Subj #2 Apr 15, 19-25, 1985; Apr 25-May 5, 1989. Subj #3 Jan 20-29, 1982; Feb 2-26, 1982, Mar 17-Apr 4, 1982, May 6-June 7, 1982; June 14-July 2, 1982.
ANALYSIS: Cosinor: single
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
ACROPHASE: Subj #1 1436 (1404, 1508) to 1700 (1444, 1916). Subj #2 1532 (1416, 1648) to 1612 (1536, 1648). Subj #3 1616 (1400, 1832) to 1756 (1632, 1920).
AMPLITUDE: Subj #1 8.95 ± 0.06 to 11.60 ± 23. Subj #2 10.54 ± 2.01 to 11.09 ± 4.46. Subj #3 5.05 ± 2.15 to 11.03 ± 4.9.
MESOR: Subj #1 82.5 ± 4.4 to 95.9 ± 1.2. Subj #2 65.2 ± 2.7 to 74.4 ± 3.9. Subj #3 77.5 ± 3.2 to 86.9 ± 3.3.
SHAPE OF WAVEFORM:
OTHER:
LIMITATIONS: small N

IMAI, et al. (1987)
SUBJECTS: Patients with Cushing's syndrome and those with hypertension Age: Gender:
VARIABLE(S): HR
METHODS: FREQUENCY:
LENGTH:
MEASUREMENT:
TIME OF YEAR:
ANALYSIS:
FINDINGS: PERIOD: Yes ___, No ___
LENGTH OF PERIOD:
PEAK: diurnal
TROUGH: nocturnal
RANGE:
MEAN:
SHAPE OF WAVEFORM:
OTHER:
LIMITATIONS: very little information in abstract. No cosinor analysis.

BIFFI, CUGINI, PELLICCIA, SPATARO, CASELLI, PIOVANO (1987)
SUBJECTS: N=10 athletes with frequent PVCs Age: 11-23 yr
Gender: N=7 males; N=3 females
VARIABLE(S): HR & PVCs
METHODS: FREQUENCY: continuous
LENGTH: 24 hr
MEASUREMENT: ECG-HR taped
TIME OF YEAR:
ANALYSIS: Cosinor: single
FINDINGS: PERIOD: Yes X, No ___ HR & PVCs (except for one subject)
LENGTH OF PERIOD: 24 hr
ACROPHASE: HR - early afternoon; PVCs - diurnal (7 of the 10 subjects)
AMPLITUDE:
MESOR:
SHAPE OF WAVEFORM:
OTHER:
LIMITATIONS: very little information in abstract.

WILLICH, LEVY, ROCCO, TOFLER, STONE, MULLER (1987)
SUBJECTS: N=429 sudden cardiac deaths outside hospital and not confined to bed. (Framingham Heart Study Data of 38 yr) Age: 69 ± 10.7 yr Gender: 65% males/ 35% females
VARIABLE(S): sudden cardiac death
METHODS: FREQUENCY: 4-6 hr intervals
LENGTH: 24 hr
MEASUREMENT: used death certificates
TIME OF YEAR:
ANALYSIS: ANOVA. Chi square - difference between intervals. T-test. 2 harmonic regression mold.
FINDINGS: PERIOD: Yes X, No ___ p<.01 Same for men and women; young and old.
LENGTH OF PERIOD: 24 hr (N=429)
PEAK: 7 AM to 9 AM
TROUGH: 9 AM to 1 PM
RANGE: 70% higher during peak than average of 22 hrs
MEAN:
SHAPE OF WAVEFORM: 2 sine and cosine functions
OTHER: SCD was evenly distributed over week and months of the year.
LIMITATIONS: exact time of death unknown. No cosinor analysis.

REBUZZI, LUCENTE, LANZA, COPPOLA, MANZOLI (1987)
SUBJECTS: N=406 in hospital (N=297 with CHD) Age: Gender:
VARIABLE(S): PVCs & VT (3 or more beats)
METHODS: FREQUENCY: continuous
LENGTH: 24 hr
MEASUREMENT: ECG. Diary kept.
TIME OF YEAR: March, 1983-May, 1984
ANALYSIS: scanner used. Cosinor: group.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr for VT
ACROPHASE: 1102 hr
AMPLITUDE: 0.59
MESOR: 1.71
SHAPE OF WAVEFORM: sinusoidal
OTHER: 41 episodes of VT in N=32 (7.88%). No significant rhythms were seen in PVCs in those with VT.
LIMITATIONS: age and gender of subjects unknown.

MULLER, et al. (1987)
SUBJECTS: N=2203 died outside hospital from MI. N=685 CHD and arrhythmia deaths outside hospital Age:
Gender:
VARIABLE(S): death due to CHD and/or arrhythmias
METHODS: FREQUENCY: continuous
LENGTH: 1 yr
MEASUREMENT: death certificates of those who died outside the hospital were used.
TIME OF YEAR: 1983, Massachusetts. Subjects died < 1 hr after onset of symptoms.
ANALYSIS: Graphic. ANOVA. 1 and 2 Harmonic regression model. Goodness of fit was evaluated with T-test (2-tailed).
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr
PEAK: 10-11 AM, 5-6 PM
TROUGH: during night
RANGE:
MEAN:
SHAPE OF WAVEFORM:
OTHER: For out of hospital deaths due to CHD and arrhythmias, N=7417, (regardless of interval from onset of symptoms) a significant circadian rhythm p<.001. Peak 7-11 AM. For inhospital deaths due to CHD and arrhythmias N=9513 (regardless of interval from onset of symptoms), death is randomly distributed over 24 hr period. Fewer deaths are seen from 2400-0600. Computed the number of sudden cardiac deaths during sleep in 7 previous studies (Total N=689). Only 85 (12.3%) deaths occurred during sleep (p<.001) vs 201 (29%) expected if SCD were randomly distributed over a 24 hr period with 7 hr sleep.
LIMITATIONS: wake/sleep cycles were unknown. No cosinor analysis.

IRWIN, MCCARTHY, WILKINSON, PRITCHETT (1988)
SUBJECTS: N=52 patients with PSVT Age: 46.2 ± 15.7 yr
Gender: N=31 males; N=21 females
VARIABLE(S): PSVT
METHODS: FREQUENCY: averaged into 2 hr intervals
LENGTH:
MEASUREMENT: no antiarrhythmic therapy. Telephone transmission of the ECG when patient was aware of arrhythmia. 1 attack from each patient and a 2nd attack in N=35.
TIME OF YEAR:
ANALYSIS: Graphic. Cosinor. Episode 1 vs Episode 2 Kolmogorov statistic.
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr
ACROPHASE: 1600
AMPLITUDE:
MESOR:
SHAPE OF WAVEFORM: sinusoidal
OTHER: Episode 1 and 2 occurred at similar times.
LIMITATIONS: cosinor analysis not presented

BOUSQUET, CHAU, PONCELET, WAREMBOURG, CARRE (1988)
SUBJECTS: N=36 untreated subjects with normal or borderline hypertension Age: 65-89 yr (74 ± 1 yr)
Gender: N=12 males; N=24 females
VARIABLE(S): HR
METHODS: FREQUENCY: 15 min intervals (0800-2145); 30 min intervals (2200-0745)
LENGTH: 24 hr
MEASUREMENT: rested in an examination room for 24 hr. Bard-Senton-HR.
TIME OF YEAR:
ANALYSIS: Fournier analysis - first 4 harmonics
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr, 12 hr, 8 hr, 6 hr
PEAK: day (0800-2200)
TROUGH: night (2200-0800)
RANGE: 5.6 to 11.7
MEAN: 76.6 ± 2.1 to 79.1 ± 2.6
SHAPE OF WAVEFORM:
OTHER: difference between day vs night, significant (p <.001)
LIMITATIONS: no cosinor analysis

BISCHOFF, et al. (1988)
SUBJECTS: N=48 patients with hyperthyroidism; N=50 NLs
Age: N=48, 23-68 yr (49 ± 11 yr); N=5, 30-66 yr (51 ± 8 yr) Gender: N=48, N=39 males; N=9 females; N=50, N=9 males; N=41 females
VARIABLE(S): HR & R
METHODS: FREQUENCY: continuous
LENGTH: 24 hr x 3 before, during, and after thyroid medicine
MEASUREMENT: ECG-HR taped
TIME OF YEAR:
ANALYSIS: scanner used. Descriptive T-test, Chi square, correlation, graphic.
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr
PEAK: 1200-2000
TROUGH: 0100-0600
RANGE: 20 beats
MEAN: NLs, 72 ± 8; Patients 79 ± 9 to 95 ± 13
SHAPE OF WAVEFORM: sinusoidal
OTHER: 6% of patients had VT; 4% of the controls on VT. Day-night difference in HR remained constant during 3 - 24 hr periods.
LIMITATIONS: no cosinor analysis

KOCOVIC, VELIMIROVIC, DJORDJEVIC, PAVLOVIC, SAVIC, STOJANOV (1988)
SUBJECTS: N=198 patients with CHD and ventricular arrhythmias
Age: 39-77 yr (56 yr) Gender:
VARIABLE(S): HR & PVCs & VT
METHODS: FREQUENCY: continuous
LENGTH: 24 hr
MEASUREMENT: no antiarrhythmic drugs. ECG-HR taped (Avionics).
TIME OF YEAR:
ANALYSIS: linear regression, descriptive and graphic. Paired T test.
FINDINGS: PERIOD: Yes _X_, No ___ HR, PVCs, Pairs of PVCs, VT
LENGTH OF PERIOD: 24 hr
PEAK: 0900 (HR); 1000-1500 (PVCs); 1000-2300 (Pairs); 0700-1200 (VT)
TROUGH: 0300 (HR); 0400 (PVCs); 0100-0400 (Pairs); 0100-0500 (VT)
RANGE: 62-81 (HR); 80% (PVCs)
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: no cosinor analysis. Unknown when subjects slept. Gender unknown.

DEGLI UBERTI, et al. (1988)
SUBJECTS: N=8 hospital patients with hypertension Age: 27-41 yr
Gender: N=3 males, N=5 females
VARIABLE(S): HR
METHODS: FREQUENCY: continuous
LENGTH: 24 hr x 2 (Before and After penbutolol)
MEASUREMENT: ECG-HR taped (Nippon). In hospital. Constant diet for 5 days prior (0730, 1130, 1530, 1900)
TIME OF YEAR:
ANALYSIS: Cosinor: single and group.
FINDINGS: PERIOD: Yes _X_, No ___ p=.011 for before only.
LENGTH OF PERIOD: 24 hr
ACROPHASE: 1416 (1056, 2241)
AMPLITUDE: 4.2 ± 40
MESOR: 72.6 ± 3.8
SHAPE OF WAVEFORM: sinusoidal (Before)
OTHER: After penbutolol the circadian rhythm of HR disappeared. (Mesor 69.4 ± 2.8; Amplitude .6; Acrophase 1904.)
LIMITATIONS: none noted

LUCENTE, et al. (1988)
SUBJECTS: N=94 patients with acute MI with one or more episodes of VT (N=47 recent MI; N=47 old MI) Age: 63 ± 10 yr
Gender: N=81 males; N=13 females
VARIABLE(S): VT
METHODS: FREQUENCY: continuous
LENGTH: 24 hr
MEASUREMENT: no antiarrhythmia drugs. ECG-HR taped (Holter).
TIME OF YEAR: May 1982 and October 1987
ANALYSIS: Cosinor: single and group, 2 harmonic regression model and T test. Chi-square.
FINDINGS: PERIOD: Yes _X_, No ___ (p=.0007)
LENGTH OF PERIOD: 24 hr
ACROPHASE: 1429 (1st group 1640, 2nd group 1239)
AMPLITUDE: 3-6 episodes
MESOR: 6.5 episodes
SHAPE OF WAVEFORM: bimodal, sinusoidal
OTHER: single harmonic model fitted data best.
LIMITATIONS: unknown when subjects slept.

IMAI, et al. (1988)
SUBJECTS: N=38 untreated patients with hypertension; N=32 treated patients with hypertension; N=12 with severe hypertension; N=11 pituitary Cushing; N=4 adrenal Cushings; N=1 ectopic ACTH; N=13 primary aldosteronism. Age: 22-65 yr Gender:
VARIABLE(S): HR
METHODS: FREQUENCY: 5 min intervals and averaged hourly
LENGTH: 24 hr
MEASUREMENT: ECG-HR taped. On a ward. Dark 2100-0600. Ate at 0730, 1130,1700.
TIME OF YEAR:
ANALYSIS: Graphic, values averaged for waking hr 0600-2059 and night time hr 2100-0559. T test. Linear regression.
FINDINGS: PERIOD: Yes _X_, No ___ All subjects
LENGTH OF PERIOD: 24 hr
PEAK: day
TROUGH: night
RANGE: 6 to 15
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: no cosinor analysis. Gender unknown.

RAEDER, HOHNLOSER, GRABOYS, PODRID, LAMPERT, LOWN (1988)
SUBJECTS: N=45 patients with a history of malignant ventricular tachyarrhythmias Age: 15-76 yr (56 yr)
Gender: N=26 males; N=19 females
VARIABLE(S): HR & PVCs
METHODS: FREQUENCY: continuous
LENGTH: 2-24 hr
MEASUREMENT: ECG-HR & R taped. No antiarrhythmic drugs.
TIME OF YEAR:
ANALYSIS: correlation, multiple regression
FINDINGS: PERIOD: Yes _X_, No ___ HR & R
LENGTH OF PERIOD: 24 hr
PEAK: 1000 - 1200 (PVCs)
TROUGH: 0500 (PVCs)
RANGE:
MEAN:
SHAPE OF WAVEFORM:
OTHER:
LIMITATIONS: no cosinor analysis

SUNDBERG, KOHVAKKA, GORDIN (1988)
SUBJECTS: N=7 normotensive healthy shift workers Age: 22-45 yr (31 yr) Gender:
VARIABLE(S): HR
METHODS: FREQUENCY: 15 min intervals during waking hr; 30 min intervals during sleep. Averaged hourly.
LENGTH: 24 hr x 3
MEASUREMENT: The first monitoring session took place at the end of an ordinary work period of morning shifts, the second on the first day of a period of night shifts, and the third on the last day of a period of night shifts. Ordinary shift, rise at 0600 hr, work from 0700 to 1500 hr, sleep from 2230 to 0600 hr (monitoring began at 0700 hr). Night shifts 1 and 2; work from 2130 to 0730, sleep from 1200 to 1700 hr (monitoring at 2130). No bath, showers, sauna, or physical activity. No alcohol. ECG-HR taped. Diaries kept.
TIME OF YEAR:
ANALYSIS: 2 way ANOVA. Graphic.
FINDINGS: PERIOD: Yes _X_, No ___
LENGTH OF PERIOD: 24 hr
PEAK: while awake
TROUGH: with sleep
RANGE: 60-80
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER: There was a trend toward a slower HR at night while subjects were at work.
LIMITATIONS: no cosinor analysis

COLQUHOUN (1988)
SUBJECTS: N=72 subjects Age: "young" Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: 2 hr intervals
LENGTH: 24 hr
MEASUREMENT: normal sleep-wake cycle without work. Awake at 0705 to 0740. Lunch 1215-1245. Radial artery palpated for 1 min.
TIME OF YEAR: 1967
ANALYSIS: Graphic.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24 hr
PEAK: 0800-2100
TROUGH: 2300-0700
RANGE: 71-84
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER:
LIMITATIONS: no cosinor analysis

COLQUHOUN, et al. (1988) and PLETT, COLQUHOUN, CONDON, KNAUTH, RUTENFRANZ, EICKHOFF (1988)
SUBJECTS: N=4 watchkeepers work a 4 hr on-8 hr off routine; N=3 day workers Age: 21-56 yr Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: continuously
LENGTH: up to 2 wk
MEASUREMENT: at sea, aboard ship. Longitudinal voyages on 5 ships. Diaries kept. ECG-HR taped (cardiocorder).
TIME OF YEAR:
ANALYSIS: Graphic: individuals
FINDINGS: PERIOD: Yes X, No ___ in dayworks and in 1 shift worker
LENGTH OF PERIOD: 24 hr
PEAK: 0800-2400
TROUGH: 2400-0800
RANGE: 65-130
MEAN:
SHAPE OF WAVEFORM: sinusoidal
OTHER: full phase adjustment of the circadian rhythm to shifted hours of work did not occur. The other two shift workers had flattened curves.
LIMITATIONS: no cosinor analysis of HR data.

VALTY ET AL. (1989)
SUBJECTS: N=181 patients N=54 were in the hospital (not ICU); N=127 were ambulatory patients Age: 19-87 yr (54.7 ± 15.6 yr) Gender: Males 111 (61%); Females 70
VARIABLE(S): HR
METHODS: FREQUENCY: continuously. Oscillometric
LENGTH: 0000 to 0600 and 0900 to 1900
MEASUREMENT: N=100 were treated for high blood pressure, day active patients. N=26 on calcium channel blockers; N=34 on beta blockers; N=42 on conversion enzyme inhibitor; N=24 on diuretics
TIME OF YEAR:
ANALYSIS: T-test, Chi square linear and non linear correlation
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24h
PEAK: day
TROUGH: night
RANGE: day - N=127 80 ± 13; N=54 77 ± 13
night N=127 66 ± 12; N=54 68 ± 12
MEAN: N=54, 79.6; N=127, 77.1
SHAPE OF WAVEFORM: not stated
OTHER:
LIMITATIONS: no cosinor analysis. No graphic display of the data.

DJORDJEVIC ET AL. (1989)
SUBJECTS: N=150 normal subjects Age: Group 1: 20-29, Group 2: 30-39, Group 3: 40-49, Group 4: 50-59, Group 5: 60-69 N=20 in each group Gender: not stated
VARIABLE(S): HR
METHODS: FREQUENCY: continuously averaged
LENGTH: hourly
MEASUREMENT: Holter monitoring (V_5 & V_6)
TIME OF YEAR: not stated
ANALYSIS: descriptive statistics; graphs
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: 24h
PEAK: 0900 & 1800
TROUGH: 0400
RANGE: 59-90
MEAN: 54-78
SHAPE OF WAVEFORM: somewhat sinusoidal
OTHER: range decreased with increasing age
LIMITATIONS: no cosinor analysis

FELVER & PIKE (1989)
SUBJECTS: N=2 physiologically unstable patients in ICU
Age: 52 and 53 yr Gender: males
VARIABLE(S): HR
METHODS: FREQUENCY: 15 min intervals from cardiac monitor
LENGTH: 24 hr
MEASUREMENT: patients on ventilators
TIME OF YEAR: August, 1988
ANALYSIS: Cosinor: single. Graphic.
FINDINGS: PERIOD: Yes X, No ___
LENGTH OF PERIOD: #1 - 24 hr ($p<.001$); 6 hr ($p<.001$);
#2 - 24 hr ($p=.076$); 3 hr ($p=0.004$).
ACROPHASE:
AMPLITUDE:
MESOR:
SHAPE OF WAVEFORM:
OTHER: Environmental variables were noted (noise level and source, tactile stimuli, therapeutic procedures, interpersonal interactions, fluid, & medications).
LIMITATIONS:

Appendix D

Background Variable Record

BACKGROUND VARIABLE RECORD

Subject Identification Number _____

Hospital ID Number _____

Date _____ Time _____ Observer _____

Date of Birth _____ Age _____ Gender _____

Height _____ Chart _____ Tape Measure _____

Weight _____ BSA _____

Race _____

Occupation _____ Work Schedule _____

Geographic Location (state) of residence _____

Hospital admission date and time _____

ICU admission date and time _____

Sensory deficits and therapeutic aids (glasses, dentures, hearing aid, prosthesis) _____

Summarize medical history on separate sheet and attach. (Including previous hospital and ICU experience)

Current medical diagnoses _____

_____

_____

Surgery - date _____ time _____ type _____

duration _____ anesthesia type _____

anesthesia duration _____ blood loss _____

fluid administered _____

medications _____

Current nursing diagnoses (from chart) _____

_____

_____

BACKGROUND VARIABLE RECORD (page 2)

Subject Identification Number _____

Date _____ Time _____ Observer _____

Medications prior to study:

at home (type, dose, route, time, duration) _____

_____

_____

in hospital (date, time, type, dose, route) _____

_____

_____

_____

_____

Level of consciousness at hospital admission _____

Level of consciousness at ICU admission (Glasgow coma score) _____

_____

Usual prehospital daily pattern (wake/sleep; meals; activity on off days)

_____

_____

Time of day preference _____

Hospital acuity score (Adm) _____ (time of ICU adm) _____

Other:

Note: Modified from a protocol used by Felver, L (1988) in Temporal Patterning of Physiological and Environmental Variable in Patients in an Intensive Care Unit.

OHSU Acuity Tool: Critical Care

DIET	0	Needs Little Assistance With Feeding/NPO	3	Feed, Tube Feed Force or Restrict Fluids		
HYGIENE/ACTIVITY	0	Assistance With Hygiene and Ambulation	4	Complete Bath, Pt. Can Assist With Turn, Amb.	6	Completely Dependent/ Total Care
ELIMINATION Incontinent/ Diaphoretic	0	Commode/Urinal	1	Bedpan/Foley	3	
MEDICATIONS/IVs	0	Oral or NG Meds 1 Infusing IVs-Heparin Lock	4	2-4 IV Pushes/Shift 2 Infusing IVs/2 or more Blood Prod./Shift Fluid Challenge	8	5 IV Pushes/Shift 3 Infusing IVs
VS/MONITORING	0	BP q 2-4°	6	BP q 1-2° plus 1-2 Major and/or 3 Minor Monitoring Modalities	10	BP q 15-30 min. 2 or more Major Plus 4 or more Minor Monitoring Modalities
TREATMENTS	0	2 Minor	2	1 Major plus 2 Minor	3	2 or more Major and/or 4 or more Minor
TEACHING/ EMOTIONAL SUPPORT	0	Routine Explanations With Normal Care Activities	2	Routine Teaching With Emotional Support For Patient With New Diagnoses Teaching for Identified Needs of Patient/ Family	4	Extraordinary Factors: Unprepared Family Life-Threatening Complications Language Barrier (ET & Trach) Patient Restrained Isolation

Name: _____ 7-3: ____ 3-11: ____ 11-7: ____

Cat. I - 0 to 9
II - 10 to 23
III - 24 to 37

TREATMENTS

Major:
- Cardioversion
- Suction
- Weaning procedure
- Ventilator
- Kenetic Rx
- Auto Transfusion
- Major Dressing Change

Minor:
- Chest PT by Nursing at least once/shift
- Pacemaker Checks
- Inspirometer by Nursing
- ROM
- Chest Tube Strip
- Air Flow & Other Spec Beds
- Gastric Lavage

MONITORING MODALITIES

Major:
- 12 Lead EKG
- Swan Ganz
- Cardiac Output
- Arterial Line
- IABP
- ICP
- Ultra Filtration
- PD
- LA Line

Minor:
- Orthostatic BP
- q 1 hour in/out
- Neuro Checks
- Pedal Pulses
- Specimen Analysis:
  - SA
  - Guaiac
  - Gastric
- Lab Draws
  - 1x/shift
- Abd Girth
- CVP
- O_2 Saturation

Glasgow Coma Scale

1. Eye Opening

Spontaneous	4
To voice	3
To pain	2
None	1

2. Verbal Response

Oriented	5
Confused	4
Inappropriate words	3
Incomprehensible sounds	2
None	1

3. Motor Response

Obeys commands	6
Purposeful (pain)	5
Withdraw (pain)	4
Flexion (pain)	3
Extension (pain)	2
None	1

Addition of highest score in each category _____

Appendix E

Status Record

STATUS RECORD

(To be completed at the beginning of each data collection shift)

Subject Identification Number _____

Date _____ Time _____ Observer _____

Air temperature at side of bed _____

Light intensity at head of bed _____

Light source: _____ Artificial _____ Natural _____ Both

Time cues within subject's field of vision: _____ Clock _____ Calendar

_____ Window _____ TV _____ Radio

Mechanical tactile stimuli:

position in bed _____

type and position of bedcovers _____

type of mattress _____

clothing _____

dressings and casts _____

external monitoring devices _____

_____

therapeutic attachments _____

_____

Fluid and Nutrient Infusions:

#1 Type _____

_____

Route _____ Rate _____

Temp: _____ C _____ R _____ W _____ H

Comments: _____

#2 Type _____

_____

Route _____ Rate _____

Temp: _____ C _____ R _____ W _____ H

Comments: _____

#3 Type _____

_____

Route _____ Rate _____

Temp: _____ C _____ R _____ W _____ H

Comments: _____

#4 Type _____

_____

Route _____ Rate _____

Temp: _____ C _____ R _____ W _____ H

Comments: _____

#5 Type _____

_____

Route _____ Rate _____

Temp: _____ C _____ R _____ W _____ H

Comments: _____

#6 Type _____

_____

Route _____ Rate _____

Temp: _____ C _____ R _____ W _____ H

Comments: _____

#7 Type _____

_____

Route _____ Rate _____

Temp: _____ C _____ R _____ W _____ H

Comments: _____

Note: C = Cold, R = Room, W = Warm, H = Hot

Oxygen: route and concentration or flow rate _____

Note: Modified from a protocol used by Felver, L (1988) in Temporal Patterning of Physiological and Environmental Variable in Patients in an Intensive Care Unit.

Appendix F

Debriefing Log

DEBRIEFING LOG

Subject Identification Number _____

Date _____ Time Span of Observation _____

Observer _____

Problems:

Suggestions:

Successes:

Other Comments:

Note: Modified from a protocol used by Felver, L (1988) in Temporal Patterning of Physiological and Environmental Variable in Patients in an Intensive Care Unit.

Appendix G

Data Collection Records

Subject ID Number _____

Page # _____

TIME (hours & mins)	DEVICES/ COVERS	MEDICATIONS	O_2 METHOD %	BODY POSITION	SELF-I MOVE	VERB SELF	TIME CUES	LIGHT FC	SLEEP/WAKE	GLASGOW COMA SCALE	LAB VALUES	OTHER

Subject ID Number ______________

TIME (hours/minutes)	EVENTS who	what	whom	pur-pose	NOISE	OTHER

CODE LIST FOR EVENTS

Who

0 loudspeaker (LD)
1 nurse (RN)
2 physician (MD)
3 respiratory therapist (RT)
4 other health professional (HP)
5 significant other (SIG)
6 other family member (FAM)
7 friend or spiritual leader (FND)
8 patient (subject) (PT)
9 other patient (OP)

What

0 hum, sing, whistle (hum)
1 talk (tlk)
2 touch (tch)
3 laugh (lgh)
4 cry or moan (cry)
5 scream (scr)
6 cough or clear throat (cgh)
7 sneeze or blow nose (snz)
8 code/arrest (cde)
9 observe (obs)

Whom

0 telephone (PH)
1 nurse (RN)
2 physician (MD)
3 respiratory therapist (RT)
4 other health professional (HP)
5 significant other (SIG)
6 other family member (FAM)
7 friend or spiritual leader (FND)
8 patient (subject) (PT)
9 equipment or not applicable (NA)

Purpose

0
1 procedure (pro)
2 comfort (cft)
3 assessment (ass)
4 give or seek information (inf)
5
6 turn (trn)
7 reposition (rpo)
8 transfer (mve)
9 not applicable (na)

Note: Purpose for vital signs is assessment.
Identify the type of procedure and the type of assessment when using these codes.

Appendix H

Data Collection Protocol

Summary Data Collection Protocol

Before observation period begins:
- Identify potential subjects
- Obtain consent
- Complete background variable record
- Complete status record (q 12^{o})
- Gather, set up, and check calibration of equipment:
  - CO computer for CO and temperature (q 12^{o})
  - IVAC thermometer (q 12^{o}); and 2 - channel temperature monitor (once)
- Insert rectal probe (q 12^{o})
- Check V_1 electrodes and placement of V_1 on channel 1 and plug in Holter tape recorder
- Synchronize watch
- Go to bathroom

As they occur:
- Record in-room events (including alarms) on Data Record
- Record physiological and environmental variables on the Data Record
- Change in lighting

Every hour on the hour
- Heart rate and rhythm
- Bladder temperature
- Rectal temperature
- PA temperature
- Ambient air temperature
- Oral temperature
- CO x 3
- Urine output (if measuring bladder temperature)
- Ventilator parameters
- Light intensity (2000 Lux)

Every hour on the quarter hour
- Heart rate and rhythm
- Bladder temperature
- Rectal temperature
- PA temperature

Every hour on the three-quarter hour
- Heart rate and rhythm
- Bladder temperature
- Rectal temperature
- PA temperature

Every hour on the half hour
- Heart rate and rhythm
- Bladder temperature
- Rectal temperature
- PA temperature

Every 24 hours
- Holter tape changes

End of shift
- debriefing log

Data Collection Protocol

1. IDENTIFY POTENTIAL SUBJECTS: Patients in the Surgical Intensive Care unit will be screened daily using the following criteria:

   Inclusion Criteria:

   -- Thermodilution PA catheter expected to be in place for for 24-48 hrs

   -- Bladder temperature probe expected to be in place for 24-48 hrs

   -- Age 18 to 70 years, males or females

   -- Patients in the Surgical Intensive Care Unit (ICU)

   Exclusion Criteria:

   -- Patients in atrial fibrillation or those with pacemakers

   -- Patients with neck injuries that involve the brain stem

   -- Patients who cannot have CO measured at least every 4 hrs

   -- Patients who are not predicted to have PA catheter and bladder probe in place for 24 to 48 hrs

   -- Patients who have been in ICU more than one week

   -- Patients who are not expected to be in ICU for at least 24 hrs

2. OBTAIN INFORMED CONSENT from the patient or patient's surrogate

3. RECORD DATA ON BACKGROUND VARIABLE RECORD

4. GATHER, SET UP, AND CHECK CALIBRATION ON ALL EQUIPMENT

   A. Holter Monitor - Heart rate and rhythm

      Frequency: at the beginning of data collection the Holter is connected to the cardiac monitor for continuous measurement for up to 48 hours

      Instruments: Holter tape recorder, tapes, cable, Hewlett Packard (HP) cardiac monitor (Model 56), chest electrodes

Protocol: at the beginning of data collection, ensure that ECG leads are in the lead V_1, and lead II positions. Attach via cable the Holter tape recorder to the analog output (synchronizer outlet) of the HP cardiac monitor. Tape and battery must be changed in 24 hours when using 24-hour tapes. Tapes will be interpreted after the completion of data collection.

B. Two-channel temperature monitor

Frequency: at the beginning of data collection and as needed

Instruments: Mon-A-Therm Model 6500 Monitor; Cath Temp Foley Catheter (in place); Mallinckrodt Disposable Esophageal/Rectal Probe; Disposable Gloves; Data Record; Lubricating Ointment

Protocol:

1. Position patient for placement of rectal probe.
2. Don gloves.
3. Lubricate insertion end of rectal probe with institution approved lubricating ointment.
4. Gently insert rectal probe 3 inches posteriorly into rectum.
5. Secure in place with tape to patient's thigh.
6. Reposition patient if necessary.
7. Remove gloves.
8. Wash hands.
9. Connect the temperature sensor contacts on the CathTemp to Site 1.

a. Open Site 1 cable connector by pressing on the back portion of toggle with your thumb.

b. Insert flat rectangular end of temperature sensor with contacts up into open connector.

c. Check for correct positioning. (Can be visually checked through clear base of the connector; rectangular end should be positioned against rear wall of connector before closing connector.)

10. Close the connector by pressing on the front portion of the toggle with your thumb until it snaps shut.

11. Press Site 2 Room Switch -- room temperature disappears from display.

12. Connect the temperature sensor contacts on the rectal probe to Site 2 (repeat Steps 9 a-c and 11).

13. Press C to display Centigrade, F to display Fahrenheit.

14. Temperatures will be updated alternately on Site 1 (rectal) then on Site 2 (ambient air) approximately every 4 seconds.

15. If OPEN appears at site instead of temperature reading, repeat Steps 9 a-c and 10. If OPEN remains on the display, replace the disposable temperature sensor at that monitoring site as there is an open or broken electrical circuit.

C. Protocol for Calibration of Two Channel Temperature Monitor

Frequency: before and after data collection each subject

Instruments: Mon-A-Therm Model 6500 Monitor

Protocol:

1. Turn the monitor on by pressing the on/off switch.
2. Monitor will automatically display 188.8 F C on each temperature site.
3. Monitor will also automatically display annunciators ALARM, OPEN, and BATT on each temperature site.
4. This calibration check mode (steps 2-3) will last for approximately 6 seconds.
5. If the unit is properly calibrated, the machine will display 100.0 $\pm$ .2^{o}F digit for approximately 3 seconds at each temperature site.
6. If the monitor fails step 5, repeat steps 1-5 by first turning the monitor off.

D. Protocol for Electronic Thermometer Calibration Check

Frequency: every 12 hours during data collection

Instruments: IVAC TempPlus Model 2000 electronic thermometer, IVAC 828A Tester (Calibration) Plug

Protocol:

1. Set the P-M switch to M (monitor mode).
2. Remove the probe connector from the probe connector socket and insert the tester in its place.
3. Remove the probe from its storage well as if taking a normal temperature.
4. Observe that the display indicates 98.6 $\pm$ 0.1 degree F with no read light or audible signal. This confirms calibration.

5. Remove the calibration tester; replace probe and probe connector.

6. Set the P-M switch to P (predictive mode).

E. Protocol for Cardiac Output Calibration Check

Frequency: every 12 hours during data collection

Instruments: Baxter Edwards Cardiac Output Computer 9520A

Protocol: SELF-TEST (this test is internal to the computer and yields no information about the cable or catheter). Refer to Figure 1 for close-ups of the COC display during SELF-TEST.

1. Push the "SELF-TEST" button.
2. Wait for display to show a series of dashes (---).
3. When the display shows "RDY", push the "START" button. The display will show "0.00".
4. If the unit is within calibration, an "OK" should appear on the display within fifteen (15) seconds.
5. If a series of dashes (---) reappear, the unit is not within calibration. Refer the unit to Edwards for maintenance.
6. "RDY" will appear in thirty (30) seconds indicating readiness for another SELF-TEST or cardiac output determination.

B_T TEST (this test yields information either about the electrical continuity within the connecting cable or the computer's ability to monitor blood temperature).

1. Remove the catheter from the cable and connect the

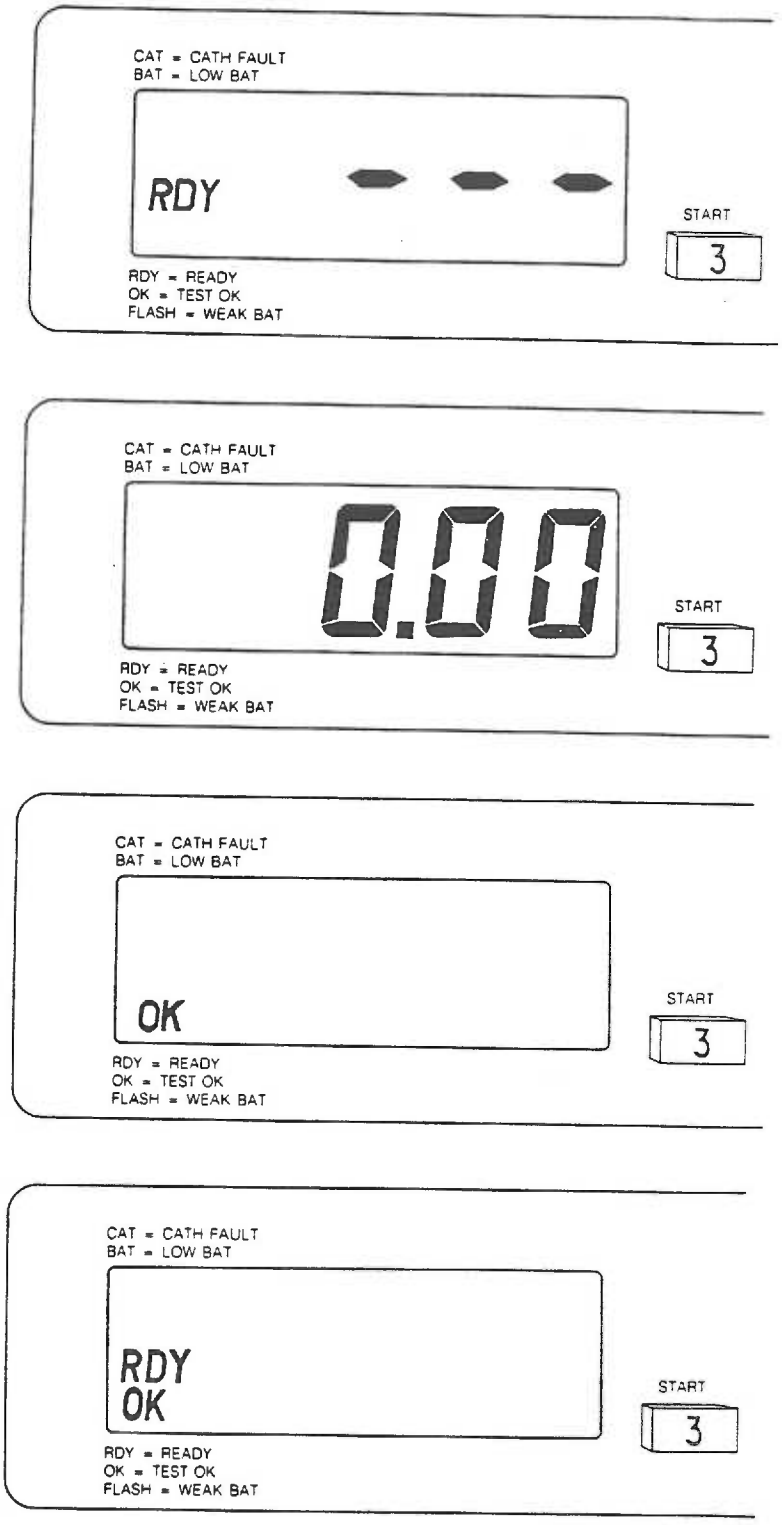


Figure 1 COC Display During Self-Test

An Acceptable "B_T Test"
Results in a Display
of 37.0° ± 0.5°C

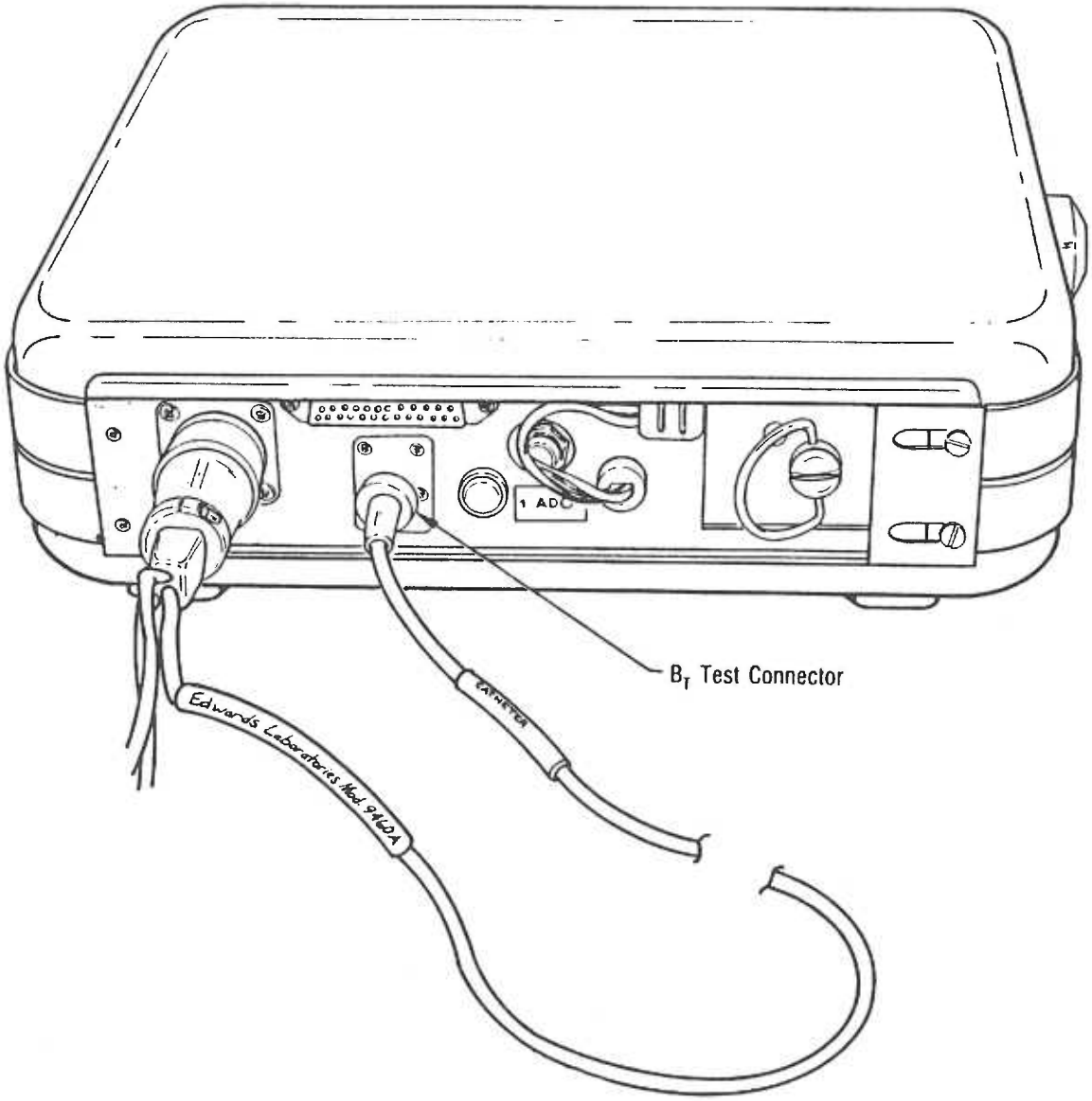


Figure 2 B_T Test Setup

cable's catheter lead to the 3-pin male, test receptacle on back of the computer. (Figure 2)

2. Push the "BLOOD TEMP" button.
3. A display of 37.0 $\pm$ 0.5°C indicates that the computer and cable are functioning properly and that the "CAT" fault is caused by the catheter circuitry. Any numerical display outside the 37.0 $\pm$ 0.5°C range indicates that the fault is in the computer or cable.

5. IMMEDIATELY BEFORE OBSERVATION PERIOD BEGINS:

-- Go to the bathroom!

-- Complete Status Record and repeat every shift.

-- Synchronize watch with time on room clock.

6. AS THEY OCCUR:

-- Record in-room events (including alarms) on the Data Record.

-- Record physiological and environmental variables on the Data Record.

7. MEASURE BLADDER TEMPERATURE

Protocol for Measurement of Bladder Temperature

Frequency: every 15 minutes

Instruments: CathTemp Foley Catheter; Mon-A-Therm Model 6500 Monitor; Data Record

Protocol:

1. Every 15 minutes note bladder temperature reading on machine display (in °C).
2. Record reading and time on Data Record.

8. MEASURE RECTAL TEMPERATURE

Protocol for Measurement of Rectal Temperature

Frequency: every 15 minutes

Instruments: Mallinckrodt Disposable Esophageal/Rectal Probe; Mon-A-Therm Model 6500 Monitor; Data Record

Protocol:

1. Every 15 minutes note rectal temperature reading on machine display (in ^{o}C).
2. Record reading and time on Data Record.

9. MEASURE AMBIENT AIR TEMPERATURE

Protocol for Measurement of Air Temperature

Frequency: every 60 minutes

Instruments: Mon-A-Therm Model 6500 monitor; Data Record

Protocol:

1. Press "Site 2 Room" switch.
2. Site 2 temperature will be replaced by room temperature.
3. Note room temperature reading in ^{o}C.
4. Record reading and time on data record.
5. Press "Site 2 Room" switch to return to Site 2 reading.

10. MEASURE PA TEMPERATURE

Protocol for Measurement of Pulmonary Artery Temperature

Frequency: every 15 minutes

Instruments: Swan-Ganz Thermodilution Catheter (Model No. 93A-131-7F/131H) or a VIP Catheter (Model No. 93A-831-7.5F/831H); Edwards Cardiac Output Computer 9520A; Data Record; Cable

Protocol:

1. Every 15 minutes note pulmonary artery temperature reading on machine display (in ^{o}C).
2. Record reading and time on Data Record.

11. MEASURE ORAL TEMPERATURE

Protocol for Measurement of Oral Temperature

Frequency: every 60 minutes

Instruments: EVAC TempPlus Model 2000 electronic thermometer; Data Record

Protocol:

1. Put on disposable gloves.
2. Remove the IVAC TempPlus from the charger.
3. Check that the P-M switch is in the P (Predictive mode).
4. Check that the F-C switch is in the C (celsius) position.
5. With your thumb and forefinger, grasp the base of the probe and withdraw it from its storage well. The TempPlus unit will now automatically turn on.
6. Insert the TempPlus blue probe completely and firmly into a probe cover to ensure a secure fit. Be careful not to press the button at the base of the probe as this might loosen or eject the probe cover.
7. Ask patient to open his or her mouth slightly. Holding the probe loosely, gently insert the probe tip and carefully slide it back under the front of the tongue, along the gumline, to the sublingual pocket.

8. Hold the probe in contact with tissue until the rotating indicator on the display stops and an audible tone sounds (approximately 24 seconds).
9. Note the temperature displayed.
10. Remove the probe from the patient's mouth.
11. Hold the probe as you would a syringe and press the ejection button at the base of the probe to eject the used probe cover into a waste container.
12. Return the probe to its storage well. The unit is now automatically off and reset.
13. Return the unit to its charger base.
14. Remove the discard gloves.
15. Record the patient's temperature and the time on the appropriate data sheet.
16. Place a new box of probe covers in the storage compartment above the display panel if necessary.

12. MEASURE CARDIAC OUTPUT

Protocol for Obtaining Thermodilution Cardiac Output

Frequency: every 1 to 4 hours (as ordered)

Instruments: CO-Set™, PA catheter, Cardiac Output Computer (9520A Edwards); Strip chart recorder (Model #9811), cable (Model 601555-1), and paper; List of CO ± 10%; Data Record; gloves (disposable)

Protocol:

Steps for the preparation of the iced-temperature injectate using the CO-Set™ and for the measurement of cardiac output are listed below.

1. Put on gloves.
2. Insert the CO-Set™ tubing into the reservoir bag of either sterile saline or dextrose and water (depending on the physician preference) and flush the system with solution;
3. clamp the tubing until ready to obtain cardiac output measurement;
4. connect 10 ml syringe to Co-Set™ tubing;
5. connect the distal end of Co-Set™ tubing to the proximal port of the Swan-Ganz® catheter;
6. connect the CO-Set™ temperature probe from cardiac output computer to the CO-Set™ tubing at the flow-through housing;
7. set the coiled segment of CO-Set™ tubing in ice bucket reservoir, allow solution to cool for 15-20 minutes;
8. validate that injectate temperature is between 8-16°C (5 ml)
9. verify the pulmonary artery waveform on the oscilloscope;
10. instruct the patient to limit movement as much as possible during the procedure;
11. connect the cardiac output computer cable to the thermistor connector on the Swan-Ganz® catheter;
12. turn the computer on;

13. dial in the appropriate computation constant depending on the type of catheter used (0.259 for 7F and 93A-431H-7.5F Catheters);
14. connect, turn the strip chart recorder on and turn switch to 5 mm/sec; (see Figure 3)
15. release the CO-Set™ tubing clamp and draw 5 ml of injectate solution into syringe;
16. reapply the CO-Set™ tubing clamp;
17. at end-expiration push the "start" button on the computer and simultaneously inject the solution within a four second period of time. Check the strip chart recorder for correct thermodilution curve;
18. record the cardiac output measurement on the data collection form. This process is repeated to 5 times to obtain 3 cardiac outputs within 10% of a median value;
19. average the three cardiac outputs and record;
20. derive cardiac index using nomogram to obtain BSA.

13. EMPTY URINE AND RECORD URINE OUTPUT EVERY HOUR. Record other output also.

14. RECORD VENTILATOR PARAMETERS EVERY HOUR

If subject is mechanically ventilated, record respiratory rate, tidal volume, and temperature of inspired air from ventilator every hour.

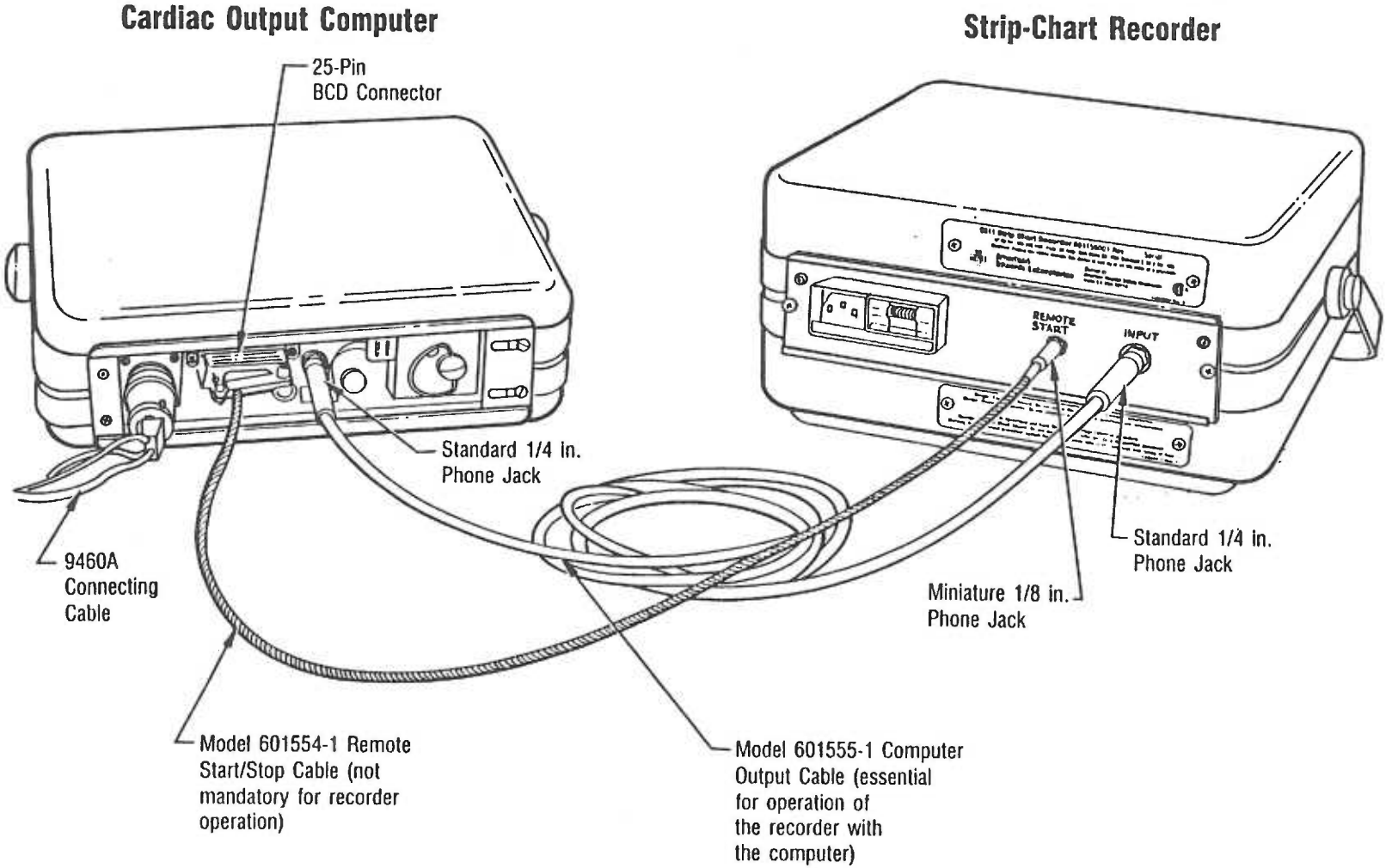


Figure 3 Computer/Recorder Interface

15. DESCRIBE PATIENT POSITION

Protocol for Measurement of Subject Position

Frequency: at beginning of each observer's shift and whenever changes

Instruments: Initial Status Record; Data Record

Operational Definitions:

The subject's position will be defined by the following categories:

1. Supine: lying on back
2. Prone: lying on stomach
3. Lying on right side
4. Lying on left side
5. Sitting on the edge of the bed
6. Sitting in a chair
7. Walking

For categories 1-4, indicate the elevation of the head of the bed in degrees.

16. RECORD FLUIDS AND NUTRITION

Protocol for Measurement of Fluid or Nutrient Temperature

Frequency: as occur

Instrument: Data Record

Operational Definitions:

1. Cold: Observer can see condensation on the outside of the container.
2. Hot: Observer can see steam rising from nutrients.

Appendix I

List of Cardiac Output Values ± 10%

C.O.	Range	C.O.	Range
1.00	0.90-1.10	1.50	1.35-1.65
.01	.91-1.11	.51	1.36-1.66
.02	.92-1.12	.52	1.37-1.67
.03	.93-1.13	.53	1.38-1.68
.04	.94-1.14	.54	1.39-1.69
.05	.95-1.15	.55	1.39-1.71
.06	.95-1.17	.56	1.40-1.72
.07	.96-1.18	.57	1.41-1.73
.08	.97-1.19	.58	1.42-1.74
.09	.98-1.20	.59	1.43-1.75
.10	.99-1.21	1.60	1.44-1.76
.11	1.00-1.22	.61	1.45-1.77
.12	1.01-1.23	.62	1.46-1.78
.13	1.02-1.24	.63	1.47-1.79
.14	1.03-1.25	.64	1.48-1.80
.15	1.03-1.27	.65	1.49-1.81
.16	1.04-1.28	.66	1.49-1.83
.17	1.05-1.29	.67	1.50-1.84
.18	1.06-1.30	.68	1.51-1.85
.19	1.07-1.31	.69	1.52-1.86
.20	1.08-1.32	1.70	1.53-1.87
.21	1.09-1.33	.71	1.54-1.88
.22	1.10-1.34	.72	1.55-1.89
.23	1.11-1.35	.73	1.56-1.90
.24	1.12-1.36	.74	1.57-1.91
.25	1.13-1.37	.75	1.57-1.93
.26	1.13-1.39	.76	1.58-1.94
.27	1.14-1.40	.77	1.59-1.95
.28	1.15-1.41	.78	1.60-1.96
.29	1.16-1.42	.79	1.61-1.97
.30	1.17-1.43	1.80	1.62-1.98
.31	1.18-1.44	.81	1.63-1.99
.32	1.19-1.45	.82	1.64-2.00
.33	1.20-1.46	.83	1.65-2.01
.34	1.21-1.47	.84	1.66-2.02
.35	1.21-1.49	.85	1.67-2.03
.36	1.22-1.50	.86	1.67-2.05
.37	1.23-1.51	.87	1.68-2.06
.38	1.24-1.52	.88	1.69-2.07
.39	1.25-1.53	.89	1.70-2.08
.40	1.26-1.54	1.90	1.71-2.09
.41	1.27-1.55	.91	1.72-2.10
.42	1.28-1.56	.92	1.73-2.11
.43	1.29-1.57	.93	1.74-2.12
.44	1.30-1.58	.94	1.75-2.13
.45	1.31-1.60	.95	1.75-2.15
.46	1.31-1.61	.96	1.76-2.16
.47	1.32-1.62	.97	1.77-2.17
.48	1.33-1.63	.98	1.78-2.18
.49	1.34-1.64	1.99	1.79-2.19

C.O.	Range	C.O.	Range
2.00	1.80-2.20	2.50	2.25-2.75
.01	1.81-2.21	.51	2.26-2.76
.02	1.82-2.22	.52	2.27-2.77
.03	1.83-2.23	.53	2.28-2.78
.04	1.84-2.24	.54	2.29-2.79
.05	1.85-2.25	.55	2.29-2.81
.06	1.85-2.27	.56	2.30-2.82
.07	1.86-2.28	.57	2.31-2.83
.08	1.87-2.29	.58	2.32-2.84
.09	1.88-2.30	.59	2.33-2.85
2.10	1.89-2.31	2.60	2.34-2.86
.11	1.90-2.32	.61	2.35-2.87
.12	1.91-2.33	.62	2.36-2.88
.13	1.92-2.34	.63	2.37-2.89
.14	1.93-2.35	.64	2.38-2.90
.15	1.93-2.37	.65	2.39-2.91
.16	1.94-2.38	.66	2.39-2.93
.17	1.95-2.39	.67	2.40-2.94
.18	1.96-2.40	.68	2.41-2.95
.19	1.97-2.41	.69	2.42-2.96
2.20	1.98-2.42	2.70	2.43-2.97
.21	1.99-2.43	.71	2.44-2.98
.22	2.00-2.44	.72	2.45-2.99
.23	2.01-2.45	.73	2.46-3.00
.24	2.02-2.46	.74	2.47-3.01
.25	2.03-2.47	.75	2.47-3.03
.26	2.03-2.49	.76	2.48-3.04
.27	2.04-2.50	.77	2.49-3.05
.28	2.05-2.51	.78	2.50-3.06
.29	2.06-2.52	.79	2.51-3.07
2.30	2.07-2.53	2.80	2.52-3.08
.31	2.08-2.54	.81	2.53-3.09
.32	2.09-2.55	.82	2.54-3.10
.33	2.10-2.56	.83	2.55-3.11
.34	2.11-2.57	.84	2.56-3.12
.35	2.11-2.59	.85	2.57-3.13
.36	2.12-2.60	.86	2.57-3.15
.37	2.13-2.61	.87	2.58-3.16
.38	2.14-2.62	.88	2.59-3.17
.39	2.15-2.63	.89	2.60-3.18
2.40	2.16-2.64	2.90	2.61-3.19
.41	2.17-2.65	.91	2.62-3.20
.42	2.18-2.66	.92	2.63-3.21
.43	2.19-2.67	.93	2.64-3.22
.44	2.20-2.68	.94	2.65-3.23
.45	2.21-2.69	.95	2.65-3.25
.46	2.21-2.71	.96	2.66-3.26
.47	2.22-2.72	.97	2.67-3.27
.48	2.23-2.73	.98	2.68-3.28
.49	2.24-2.74	2.99	2.69-3.29

C.D.	Range	C.D.	Range
3.00	2.70-3.30	3.50	3.15-3.85
.01	2.71-3.31	.51	3.16-3.86
.02	2.72-3.32	.52	3.17-3.87
.03	2.73-3.33	.53	3.18-3.88
.04	2.74-3.34	.54	3.19-3.89
.05	2.75-3.35	.55	3.19-3.91
.06	2.75-3.37	.56	3.20-3.92
.07	2.76-3.38	.57	3.21-3.93
.08	2.77-3.39	.58	3.22-3.94
.09	2.78-3.40	.59	3.23-3.95
3.10	2.79-3.41	3.60	3.24-3.96
.11	2.80-3.42	.61	3.25-3.97
.12	2.81-3.43	.62	3.26-3.98
.13	2.82-3.44	.63	3.27-3.99
.14	2.83-3.45	.64	3.28-4.00
.15	2.83-3.47	.65	3.29-4.01
.16	2.84-3.48	.66	3.29-4.03
.17	2.85-3.49	.67	3.30-4.04
.18	2.86-3.50	.68	3.31-4.05
.19	2.87-3.51	.69	3.32-4.06
3.20	2.88-3.52	3.70	3.33-4.07
.21	2.89-3.53	.71	3.34-4.08
.22	2.90-3.54	.72	3.35-4.09
.23	2.91-3.55	.73	3.35-4.10
.24	2.92-3.56	.74	3.37-4.11
.25	2.93-3.57	.75	3.37-4.13
.26	2.93-3.59	.76	3.38-4.14
.27	2.94-3.60	.77	3.39-4.15
.28	2.95-3.61	.78	3.40-4.16
.29	2.96-3.62	.79	3.41-4.17
3.30	2.97-3.63	3.80	3.42-4.18
.31	2.98-3.64	.81	3.43-4.19
.32	2.99-3.65	.82	3.44-4.20
.33	3.00-3.66	.83	3.45-4.21
.34	3.01-3.67	.84	3.46-4.22
.35	3.01-3.69	.85	3.47-4.23
.36	3.02-3.70	.86	3.47-4.25
.37	3.03-3.71	.87	3.48-4.26
.38	3.04-3.72	.88	3.49-4.27
.39	3.05-3.73	.89	3.50-4.28
3.40	3.06-3.74	3.90	3.51-4.29
.41	3.07-3.75	.91	3.52-4.30
.42	3.08-3.76	.92	3.53-4.31
.43	3.09-3.77	.93	3.54-4.32
.44	3.10-3.78	.94	3.55-4.33
.45	3.11-3.79	.95	3.55-4.35
.46	3.11-3.81	.96	3.56-4.36
.47	3.12-3.82	.97	3.57-4.37
.48	3.13-3.83	.98	3.58-4.38
.49	3.14-3.84	3.99	3.59-4.39

C.D.	Range	C.D.	Range
4.00	3.60-4.40	4.50	4.05-4.95
.01	3.61-4.41	.51	4.06-4.96
.02	3.62-4.42	.52	4.07-4.97
.03	3.63-4.43	.53	4.08-4.98
.04	3.64-4.44	.54	4.09-4.99
.05	3.65-4.45	.55	4.09-5.01
.06	3.65-4.47	.56	4.10-5.02
.07	3.66-4.48	.57	4.11-5.03
.08	3.67-4.49	.58	4.12-5.04
.09	3.68-4.50	.59	4.13-5.05
4.10	3.69-4.51	4.60	4.14-5.06
.11	3.70-4.52	.61	4.15-5.07
.12	3.71-4.53	.62	4.16-5.08
.13	3.72-4.54	.63	4.17-5.09
.14	3.73-4.55	.64	4.18-5.10
.15	3.73-4.57	.65	4.19-5.11
.16	3.74-4.58	.66	4.19-5.13
.17	3.75-4.59	.67	4.20-5.14
.18	3.76-4.60	.68	4.21-5.15
.19	3.77-4.61	.69	4.22-5.16
4.20	3.78-4.62	4.70	4.23-5.17
.21	3.79-4.63	.71	4.24-5.18
.22	3.80-4.64	.72	4.25-5.19
.23	3.81-4.65	.73	4.26-5.20
.24	3.82-4.66	.74	4.27-5.21
.25	3.83-4.67	.75	4.27-5.23
.26	3.83-4.69	.76	4.28-5.24
.27	3.84-4.70	.77	4.29-5.25
.28	3.85-4.71	.73	4.30-5.26
.29	3.86-4.72	.79	4.31-5.27
4.30	3.87-4.73	4.80	4.32-5.28
.31	3.88-4.74	.81	4.33-5.29
.32	3.89-4.75	.82	4.34-5.30
.33	3.90-4.76	.83	4.35-5.31
.34	3.91-4.77	.84	4.36-5.32
.35	3.91-4.79	.85	4.37-5.33
.36	3.92-4.80	.86	4.37-5.35
.37	3.93-4.81	.87	4.38-5.36
.38	3.94-4.82	.88	4.39-5.37
.39	3.95-4.83	.89	4.40-5.38
4.40	3.95-4.84	4.90	4.41-5.39
.41	3.97-4.85	.91	4.42-5.40
.42	3.98-4.86	.92	4.43-5.41
.43	3.99-4.87	.93	4.44-5.42
.44	4.00-4.88	.94	4.45-5.43
.45	4.01-4.89	.95	4.45-5.45
.46	4.01-4.91	.96	4.46-5.46
.47	4.02-4.92	.97	4.47-5.47
.48	4.03-4.93	.98	4.48-5.48
.49	4.04-4.94	4.99	4.49-5.49

C.O.	Range	C.O.	Range
5.00	4.50-5.50	5.50	4.95-6.05
.01	4.51-5.51	.51	4.96-6.06
.02	4.52-5.52	.52	4.97-6.07
.03	4.53-5.53	.53	4.98-6.08
.04	4.54-5.54	.54	4.99-6.09
.05	4.55-5.55	.55	4.99-6.11
.06	4.55-5.57	.56	5.00-6.12
.07	4.56-5.58	.57	5.01-6.13
.08	4.57-5.59	.58	5.02-6.14
.09	4.58-5.60	.59	5.03-6.15
5.10	4.59-5.61	5.60	5.04-6.16
.11	4.60-5.62	.61	5.05-6.17
.12	4.61-5.63	.62	5.06-6.18
.13	4.62-5.64	.63	5.07-6.19
.14	4.63-5.65	.64	5.08-6.20
.15	4.63-5.67	.65	5.09-6.21
.16	4.64-5.68	.66	5.09-6.23
.17	4.65-5.69	.67	5.10-6.24
.18	4.66-5.70	.68	5.11-6.25
.19	4.67-5.71	.69	5.12-6.26
5.20	4.68-5.72	5.70	5.13-6.27
.21	4.69-5.73	.71	5.14-6.28
.22	4.70-5.74	.72	5.15-6.29
.23	4.71-5.75	.73	5.16-6.30
.24	4.72-5.76	.74	5.17-6.31
.25	4.73-5.77	.75	5.17-6.33
.26	4.73-5.79	.76	5.18-6.34
.27	4.74-5.80	.77	5.19-6.35
.28	4.75-5.81	.78	5.20-6.36
.29	4.76-5.82	.79	5.21-6.37
5.30	4.77-5.83	5.80	5.22-6.38
.31	4.78-5.84	.81	5.23-6.39
.32	4.79-5.85	.82	5.24-6.40
.33	4.80-5.86	.83	5.25-6.41
.34	4.81-5.87	.84	5.26-6.42
.35	4.81-5.89	.85	5.27-6.43
.36	4.82-5.90	.86	5.27-6.45
.37	4.83-5.91	.87	5.28-6.46
.38	4.84-5.92	.88	5.29-6.47
.39	4.85-5.93	.89	5.30-6.48
5.40	4.86-5.94	5.90	5.31-6.49
.41	4.87-5.95	.91	5.32-6.50
.42	4.88-5.96	.92	5.33-6.51
.43	4.89-5.97	.93	5.34-6.52
.44	4.90-5.98	.94	5.35-6.53
.45	4.91-5.99	.95	5.35-6.55
.46	4.91-6.01	.96	5.36-6.56
.47	4.92-6.02	.97	5.37-6.57
.48	4.93-6.03	.98	5.38-6.58
.49	4.94-6.04	5.99	5.39-6.59

C.O.	Range	C.O.	Range
6.00	5.40-6.60	6.50	5.85-7.15
.01	5.41-6.61	.51	5.86-7.16
.02	5.42-6.62	.52	5.87-7.17
.03	5.43-6.63	.53	5.88-7.18
.04	5.44-6.64	.54	5.89-7.19
.05	5.45-6.65	.55	5.89-7.21
.06	5.45-6.67	.56	5.90-7.22
.07	5.46-6.68	.57	5.91-7.23
.08	5.47-6.69	.58	5.92-7.24
.09	5.48-6.70	.59	5.93-7.25
6.10	5.49-6.71	6.60	5.94-7.26
.11	5.50-6.72	.61	5.95-7.27
.12	5.51-6.73	.62	5.96-7.28
.13	5.52-6.74	.63	5.97-7.29
.14	5.53-6.75	.64	5.98-7.30
.15	5.53-6.77	.65	5.99-7.31
.16	5.54-6.78	.66	5.99-7.33
.17	5.55-6.79	.67	6.00-7.34
.18	5.56-6.80	.68	6.01-7.35
.19	5.57-6.81	.69	6.02-7.36
6.20	5.58-6.82	6.70	6.03-7.37
.21	5.59-6.83	.71	6.04-7.38
.22	5.60-6.84	.72	6.05-7.39
.23	5.61-6.85	.73	6.06-7.40
.24	5.62-6.86	.74	6.07-7.41
.25	5.63-6.87	.75	6.07-7.43
.26	5.63-6.89	.76	6.08-7.44
.27	5.64-6.90	.77	6.09-7.45
.28	5.65-6.91	.78	6.10-7.46
.29	5.66-6.92	.79	6.11-7.47
6.30	5.67-6.93	6.80	6.12-7.48
.31	5.68-6.94	.81	6.13-7.49
.32	5.69-6.95	.82	6.14-7.50
.33	5.70-6.96	.83	6.15-7.51
.34	5.71-6.97	.84	6.16-7.52
.35	5.71-6.99	.85	6.17-7.53
.36	5.72-7.00	.86	6.17-7.55
.37	5.73-7.01	.87	6.18-7.56
.38	5.74-7.02	.88	6.19-7.57
.39	5.75-7.03	.89	6.20-7.58
6.40	5.76-7.04	6.90	6.21-7.59
.41	5.77-7.05	.91	6.22-7.60
.42	5.78-7.06	.92	6.23-7.61
.43	5.79-7.07	.93	6.24-7.62
.44	5.80-7.08	.94	6.25-7.63
.45	5.81-7.09	.95	6.25-7.65
.46	5.81-7.11	.96	6.26-7.66
.47	5.82-7.12	.97	6.27-7.67
.48	5.83-7.13	.98	6.28-7.68
.49	5.84-7.14	6.99	6.29-7.69

C.O.	Range	C.O.	Range	C.O.	Range	C.O.	Range
7.00	6.30-7.70	7.50	6.75-8.25	8.00	7.20-8.80	8.50	7.65-9.35
.01	6.31-7.71	.51	6.76-8.26	.01	7.21-8.81	.51	7.66-9.36
.02	6.32-7.72	.52	6.77-8.27	.02	7.22-8.82	.52	7.67-9.37
.03	6.33-7.73	.53	6.78-8.28	.03	7.23-8.83	.53	7.68-9.38
.04	6.34-7.74	.54	6.79-8.29	.04	7.24-8.84	.54	7.69-9.39
.05	6.35-7.75	.55	6.79-8.31	.05	7.25-8.85	.55	7.69-9.41
.06	6.35-7.77	.56	6.80-8.32	.06	7.25-8.87	.56	7.70-9.42
.07	6.36-7.78	.57	6.81-8.33	.07	7.26-8.88	.57	7.71-9.43
.08	6.37-7.79	.58	6.82-8.34	.08	7.27-8.89	.58	7.72-9.44
.09	6.38-7.80	.59	6.83-8.35	.09	7.28-8.90	.59	7.73-9.45
7.10	6.39-7.81	7.60	6.84-8.36	8.10	7.29-8.91	8.60	7.74-9.46
.11	6.40-7.82	.61	6.85-8.37	.11	7.30-8.92	.61	7.75-9.47
.12	6.41-7.83	.62	6.86-8.38	.12	7.31-8.93	.62	7.76-9.48
.13	6.42-7.84	.63	6.87-8.39	.13	7.32-8.94	.63	7.77-9.49
.14	6.43-7.85	.64	6.88-8.40	.14	7.33-8.95	.64	7.78-9.50
.15	6.43-7.87	.65	6.89-8.41	.15	7.33-8.97	.65	7.79-9.51
.16	6.44-7.88	.66	6.89-8.43	.16	7.34-8.98	.66	7.79-9.53
.17	6.45-7.89	.67	6.90-8.44	.17	7.35-8.99	.67	7.80-9.54
.18	6.46-7.90	.68	6.91-8.45	.18	7.36-9.00	.68	7.81-9.55
.19	6.47-7.91	.69	6.92-8.45	.19	7.37-9.01	.69	7.82-9.56
7.20	6.48-7.92	7.70	6.9308.47	8.20	7.38-9.02	8.70	7.83-9.57
.21	6.49-7.93	.71	6.94-8.48	.21	7.39-9.03	.71	7.84-9.58
.22	6.50-7.94	.72	6.95-8.49	.22	7.40-9.04	.72	7.85-9.59
.23	6.51-7.95	.73	6.96-8.50	.23	7.41-9.05	.73	7.06-9.60
.24	6.52-7.96	.74	6.97-8.51	.24	7.42-9.06	.74	7.87-9.61
.25	6.53-7.97	.75	6.97-8.53	.25	7.43-9.07	.75	7.87-9.63
.26	6.53-7.99	.76	6.98-8.54	.26	7.43-9.09	.76	7.88-9.64
.27	6.54-8.00	.77	6.99-8.55	.27	7.44-9.10	.77	7.89-9.65
.28	6.55-8.01	.78	7.00-8.56	.28	7.45-9.11	.78	7.90-9.66
.29	6.56-8.02	.79	7.01-8.57	.29	7.46-9.12	.79	7.91-9.67
7.30	6.57-8.03	7.80	7.02-8.58	8.30	7.47-9.13	8.80	7.92-9.68
.31	6.58-8.04	.81	7.03-8.59	.31	7.48-9.14	.81	7.93-9.69
.32	6.59-8.05	.82	7.04-8.60	.32	7.49-9.15	.82	7.94-9.70
.33	6.60-8.06	.83	7.05-8.61	.33	7.50-9.16	.83	7.95-9.71
.34	6.61-8.07	.84	7.06-8.62	.34	7.51-9.17	.84	7.96-9.72
.35	6.61-8.09	.85	7.07-8.63	.35	7.51-9.19	.85	7.97-9.73
.36	6.62-8.10	.86	7.07-8.65	.36	7.52-9.20	.86	7.97-9.75
.37	6.63-8.11	.87	7.08-8.66	.37	7.53-9.21	.87	7.98-9.76
.38	6.64-8.12	.88	7.09-8.67	.38	7.54-9.22	.88	7.99-9.77
.39	6.65-8.13	.89	7.10-8.68	.39	7.55-9.23	.89	8.00-9.78
7.40	6.66-8.14	7.90	7.11-8.69	8.40	7.56-9.24	8.90	8.01-9.79
.41	6.67-8.15	.91	7.12-8.70	.41	7.57-9.25	.91	8.02-9.80
.42	6.68-8.16	.92	7.13-8.71	.42	7.58-9.26	.92	8.03-9.81
.43	6.69-8.17	.93	7.14-8.72	.43	7.59-9.27	.93	8.04-9.82
.44	6.70-8.18	.94	7.15-8.73	.44	7.60-9.28	94	8.05-9.83
.45	6.71-8.19	.95	7.15-8.75	.45	7.61-9.29	.95	8.05-9.85
.46	6.71-8.21	.96	7.16-8.76	.46	7.61-9.31	.96	8.06-9.86
.47	6.72-8.22	.97	7.17-8.77	.47	7.62-9.32	.97	8.07-9.87
.48	6.73-8.23	.98	7.18-8.78	.48	7.63-9.33	.98	8.08-9.88
.49	6.74-8.24	7.99	7.19-8.79	.49	7.64-9.34	8.99	8.09-9.89

C.O.	Range	C.O.	Range
9.00	8.10-9.90	9.50	8.55-10.45
.01	8.11-9.91	.51	8.56-10.46
.02	8.12-9.92	.52	8.57-10.47
.03	8.13-9.93	.53	8.58-10.48
.04	8.14-9.94	.54	8.59-10.49
.05	8.15-9.95	.55	8.59-10.51
.06	8.15-9.97	.56	8.60-10.52
.07	8.16-9.98	.57	8.61-10.53
.08	8.17-9.99	.58	8.62-10.54
.09	8.18-10.00	.59	8.63-10.55
9.10	8.19-10.01	9.60	8.64-10.56
.11	8.20-10.02	.61	8.65-10.57
.12	8.21-10.03	.62	8.66-10.58
.13	8.22-10.04	.63	8.67-10.59
.14	8.23-10.05	.64	8.68-10.60
.15	8.23-10.07	.65	8.69-10.61
.16	8.24-10.08	.66	8.69-10.63
.17	8.25-10.09	.67	8.70-10.64
.18	8.26-10.10	.68	8.71-10.65
.19	8.27-10.11	.69	8.72-10.66
9.20	8.28-10.12	9.70	8.73-10.67
.21	8.29-10.13	.71	8.74-10.68
.22	8.30-10.14	.72	8.75-10.69
.23	8.31-10.15	.73	8.76-10.70
.24	8.32-10.16	.74	8.77-10.71
.25	8.33-10.17	.75	8.77-10.73
.26	8.33-10.19	.76	8.78-10.74
.27	8.34-10.20	.77	8.79-10.75
.28	8.35-10.21	.78	8.80-10.76
.29	8.36-10.22	.79	8.81-10.77
9.30	8.37-10.23	9.80	8.82-10.78
.31	8.38-10.24	.81	8.83-10.79
.32	8.39-10.25	.82	8.84-10.80
.33	8.40-10.26	.83	8.85-10.81
.34	8.41-10.27	.84	8.86-10.82
.35	8.41-10.29	.85	8.87-10.83
.36	8.42-10.30	.86	8.87-10.85
.37	8.43-10.31	.87	8.88-10.86
.38	8.44-10.32	.88	8.89-10.87
.39	8.45-10.33	.89	8.90-10.88
9.40	8.46-10.34	9.90	8.91-10.89
.41	8.47-10.35	.91	8.92-10.90
.42	8.48-10.36	.92	8.93-10.91
.43	8.49-10.37	.93	8.94-10.92
.44	8.50-10.38	.94	8.95-10.93
.45	8.51-10.39	.95	8.95-10.95
.46	8.51-10.41	.96	8.96-10.96
.47	8.52-10.42	.97	8.97-10.97
.48	8.53-10.43	.98	8.98-10.98
.49	8.54-10.44	9.99	8.99-10.99

C.O.	Range	C.O.	Range
10.00	9.00-11.00	10.50	9.45-11.55
.01	9.01-11.01	.51	9.46-11.56
.02	9.02-11.02	.52	9.47-11.57
.03	9.03-11.03	.53	9.48-11.58
.04	9.04-11.04	.54	9.49-11.59
.05	9.05-11.05	.55	9.49-11.61
.06	9.05-11.07	.56	9.50-11.62
.07	9.06-11.08	.57	9.51-11.63
.08	9.07-11.09	.58	9.52-11.64
.09	9.08-11.10	.59	9.53-11.65
10.10	9.09-11.11	10.60	9.54-11.66
.11	9.10-11.12	.61	9.55-11.67
.12	9.11-11.13	.62	9.56-11.68
.13	9.12-11.14	.63	9.57-11.69
.14	9.13-11.15	.64	9.58-11.70
.15	9.13-11.17	.65	9.59-11.71
.16	9.14-11.18	.66	9.59-11.73
.17	9.15-11.19	.67	9.60-11.74
.18	9.16-11.20	.68	9.61-11.75
.19	9.17-11.21	.69	9.62-11.76
10.20	9.18-11.22	10.70	9.63-11.77
.21	9.19-11.23	.71	9.64-11.78
.22	9.20-11.24	.72	9.65-11.79
.23	9.21-11.25	.73	9.66-11.80
.24	9.22-11.26	.74	9.67-11.81
.25	9.23-11.27	.75	9.67-11.83
.26	9.23-11.29	.76	9.68-11.84
.27	9.24-11.30	.77	9.69-11.85
.28	9.25-11.31	.78	9.70-11.86
.29	9.26-11.32	.79	9.71-11.87
10.30	9.27-11.33	10.80	9.72-11.88
.31	9.28-11.34	.81	9.73-11.89
.32	9.29-11.35	.82	9.74-11.90
.33	9.30-11.36	.83	9.75-11.91
.34	9.31-11.37	.84	9.76-11.92
.35	9.31-11.39	.85	9.77-11.93
.36	9.32-11.40	.86	9.77-11.95
.37	9.33-11.41	.87	9.78-11.96
.38	9.34-11.42	.88	9.79-11.97
.39	9.35-11.43	.89	9.80-11.98
10.40	9.36-11.44	10.90	9.81-11.99
.41	9.37-11.45	.91	9.82-12.00
.42	9.38-11.46	.92	9.83-12.01
.43	9.39-11.47	.93	9.84-12.02
.44	9.40-11.48	.94	9.85-12.03
.45	9.41-11.49	.95	9.85-12.05
.46	9.41-11.51	.96	9.86-12.06
.47	9.42-11.52	.97	9.87-12.07
.48	9.43-11.53	.98	9.88-12.08
.49	9.44-11.54	10.99	9.89-12.09

C.O.	Range	C.O.	Range
11.00	9.90-12.10	11.50	10.35-12.65
.01	9.91-12.11	.51	10.36-12.66
.02	9.92-12.12	.52	10.37-12.67
.03	9.93-12.13	.53	10.38-12.68
.04	9.94-12.14	.54	10.39-12.69
.05	9.95-12.15	.55	10.39-12.71
.06	9.95-12.17	.56	10.40-12.72
.07	9.96-12.18	.57	10.41-12.73
.08	9.97-12.19	.58	10.42-12.74
.09	9.98-12.20	.59	10.43-12.75
11.10	9.99-12.21	11.60	10.44-12.76
.11	10.00-12.22	.61	10.45-12.77
.12	10.01-12.23	.62	10.46-12.78
.13	10.02-12.24	.63	10.47-12.79
.14	10.03-12.25	.64	10.48-12.80
.15	10.03-12.27	.65	10.49-12.81
.16	10.04-12.28	.66	10.49-12.83
.17	10.05-12.29	.67	10.50-12.84
.18	10.06-12.30	.68	10.51-12.85
.19	10.07-12.31	.69	10.52-12.85
11.20	10.08-12.32	11.70	10.53-12.87
.21	10.09-12.33	.71	10.54-12.88
.22	10.10-12.34	.72	10.55-12.89
.23	10.11-12.35	.73	10.56-12.90
.24	10.12-12.36	.74	10.57-12.91
.25	10.13-12.37	.75	10.57-12.93
.26	10.13-12.39	.76	10.58-12.94
.27	10.14-12.40	.77	10.59-12.95
.28	10.15-12.41	.78	10.60-12.96
.29	10.16-12.42	.79	10.61-12.97
11.30	10.17-12.43	11.80	10.62-12.98
.31	10.18-12.44	.81	10.63-12.99
.32	10.19-12.45	.82	10.64-13.00
.33	10.20-12.46	.83	10.65-13.01
.34	10.21-12.47	.84	10.66-13.02
.35	10.21-12.49	.85	10.67-13.03
.36	10.22-12.50	.86	10.67-13.05
.37	10.23-12.51	.87	10.68-13.06
.38	10.24-12.52	.88	10.69-13.07
.39	10.25-12.53	.89	10.70-13.08
11.40	10.26-12.54	11.90	10.71-13.09
.41	10.27-12.55	.91	10.72-13.10
.42	10.28-12.56	.92	10.73-13.11
.43	10.29-12.57	.93	10.74-13.12
.44	10.30-12.58	.94	10.75-13.13
.45	10.31-12.59	.95	10.75-13.15
.46	10.31-12.61	.96	10.76-13.16
.47	10.32-12.62	.97	10.77-13.17
.48	10.33-12.63	.98	10.78-13.18
.49	10.34-12.64	11.99	10.79-13.19

C.O.	Range	C.O.	Range
12.00	10.80-13.20	12.50	11.25-13.75
.01	10.81-13.21	.51	11.26-13.76
.02	10.82-13.22	.52	11.27-13.77
.03	10.83-13.23	.53	11.28-13.78
.04	10.84-13.24	.54	11.29-13.79
.05	10.85-13.25	.55	11.29-13.81
.06	10.85-13.27	.56	11.30-13.82
.07	10.86-13.28	.57	11.31-13.83
.08	10.87-13.29	.58	11.32-13.84
.09	10.88-13.30	.59	11.33-13.85
12.10	10.89-13.31	12.60	11.34-13.86
.11	10.90-13.32	.61	11.35-13.87
.12	10.91-13.33	.62	11.36-13.88
.13	10.92-13.34	.63	11.37-13.89
.14	10.93-13.35	.64	11.38-13.90
.15	10.93-13.37	.65	11.39-13.91
.16	10.94-13.38	.66	11.39-13.93
.17	10.95-13.39	.67	11.40-13.94
.18	10.96-13.40	.68	11.41-13.95
.19	10.97-13.41	.69	11.42-13.96
12.20	10.98-13.42	12.70	11.43-13.97
.21	10.99-13.43	.71	11.44-13.98
.22	11.00-13.44	.72	11.45-13.99
.23	11.01-13.45	.73	11.46-14.00
.24	11.02-13.46	.74	11.47-14.01
.25	11.03-13.47	.75	11.47-14.03
.26	11.03-13.49	.76	11.48-14.04
.27	11.04-13.50	.77	11.49-14.05
.28	11.05-13.51	.78	11.50-14.06
.29	11.06-13.52	.79	11.51-14.07
12.30	11.07-13.53	12.80	11.52-14.08
.31	11.08-13.54	.81	11.53-14.09
.32	11.09-13.55	.82	11.54-14.10
.33	11.10-13.56	.83	11.55-14.11
.34	11.11-13.57	.84	11.56-14.12
.35	11.11-13.59	.85	11.57-14.13
.36	11.12-13.60	.86	11.57-14.15
.37	11.13-13.61	.87	11.58-14.16
.38	11.14-13.62	.88	11.59-14.17
.39	11.15-13.63	.89	11.60-14.18
12.40	11.16-13.64	12.90	11.61-14.19
.41	11.17-13.65	.91	11.62-14.20
.42	11.18-13.66	.92	11.63-14.21
.43	11.19-13.67	.93	11.64-14.22
.44	11.20-13.68	.94	11.65-14.23
.45	11.21-13.69	.95	11.65-14.25
.46	11.21-13.71	.96	11.66-14.26
.47	11.22-13.72	.97	11.67-14.27
.48	11.23-13.73	.98	11.68-14.28
.49	11.24-13.74	12.99	11.69-14.29

Appendix J

Consent Form

OREGON HEALTH SCIENCES UNIVERSITY

Consent Form

Date of approval: 10-11-89

TITLE - Temporal Patterns of Temperature, Heart Rate and Rhythm, Stroke Volume, and Cardiac Output in Acutely Ill Adults in an Intensive Care Unit

PRINCIPAL INVESTIGATORS - Susan L. Woods, M.N., R.N. 206-545-2266
Renee Hoeksel, M.N., R.N. 503-775-2559
Linda Felver, Ph.D., R.N. 503-279-7839

PURPOSE

The purpose of this research study is to describe changes in selected vital signs (body temperature, heart rate and rhythm, and the amount of blood the heart pumps) for 24 to 48 hours in ill adults who are patients in the surgical intensive care unit. This study will help nurses understand more about physiological changes over time in patients in the intensive care unit and the responses of patients in the intensive care unit environment.

PROCEDURES

As part of your routine care you have had a catheter (thin tube) placed through a vein into your heart. With this heart catheter, temperature of blood near your heart and the amount of blood the heart pumps are routinely measured. Also your heart rate and rhythm are being measured continuously on a cardiac monitor. You also have a catheter in your bladder that allows temperature measurement.

For purposes of this research study, one research nurse will observe you continuously for 24 to 48 hours while you are in the intensive care unit. The research nurse will not interfere with your nursing care. She will obtain the routine measures of the amount of blood your heart pumps. This measurement will be obtained hourly or as ordered by your physician. Your heart rate and rhythm will be tape recorded from your cardiac monitor. Temperature from your bladder and from the blood next to your heart will be recorded every 15 minutes from the monitor screens. A thin flexible rectal probe will be inserted 3 inches into your rectum and taped to your leg to secure it. This probe will continuously measure rectal temperature which the research nurse will record every 15 minutes from the monitor screen. Oral temperature will be measured every hour. You will not be awakened between midnight and 5 AM for this measurement. All these measurements are part of regular care except for the rectal probe. In addition to these vital signs, the research nurse will observe the lighting, noise, and other environment events. The research nurse will obtain information from

your chart about your medical history and current condition and will ask you about your usual sleep-wake patterns and your preferred daily schedule.

RISKS

A potential inconvenience to you from this study, is that an investigator will be present in your room for 24 to 48 hours in order to collect the data.

BENEFITS

You may not personally benefit from participating in this study, but by serving as a subject, you may contribute new information which may benefit patients in the future. With a description of changes in these vital signs in ill adults, future therapies could be timed more appropriately.

CONFIDENTIALITY

Information concerning you will be kept strictly confidential. Neither your name nor your identity will be used for publication or publicity purposes. All data collection records will be given a code number and your name will not appear. The coded data will be kept indefinitely and may be used for further analysis.

COSTS

There are no costs to you for being in this study. However, you are responsible for all hospital costs.

LIABILITY

It is not the policy of the U.S. Department of Health and Human Services or any agency funding the research project in which you are participating to compensate or provide medical treatment for human subjects in the event the research results in physical injury. The Oregon Health Sciences University, as an agency of the State, is covered by the State Liability Fund. If you suffer any injury from the research project, compensation would be available to you only if you establish that the injury occurred through the fault of the University, its officers or employees. If you have further questions, please call Dr. Michael Baird at (503) 279-8014.

Other

Susan Woods or Renee Hoeksel has offered to answer any questions you might have. (Their telephone numbers are listed on page 1). Your participation is voluntary. You may refuse to participate, or you may withdraw from this study at any time without affecting your relationship

with or treatment at the Oregon Health Sciences University Hospital. Your participation in this study may be terminated if the catheters are removed prior to 24 hour time of data collection. You will receive a copy of the consent form. Your signature below indicates that you have read the foregoing and agree to participate in this study.

_____ _____
Subject Date

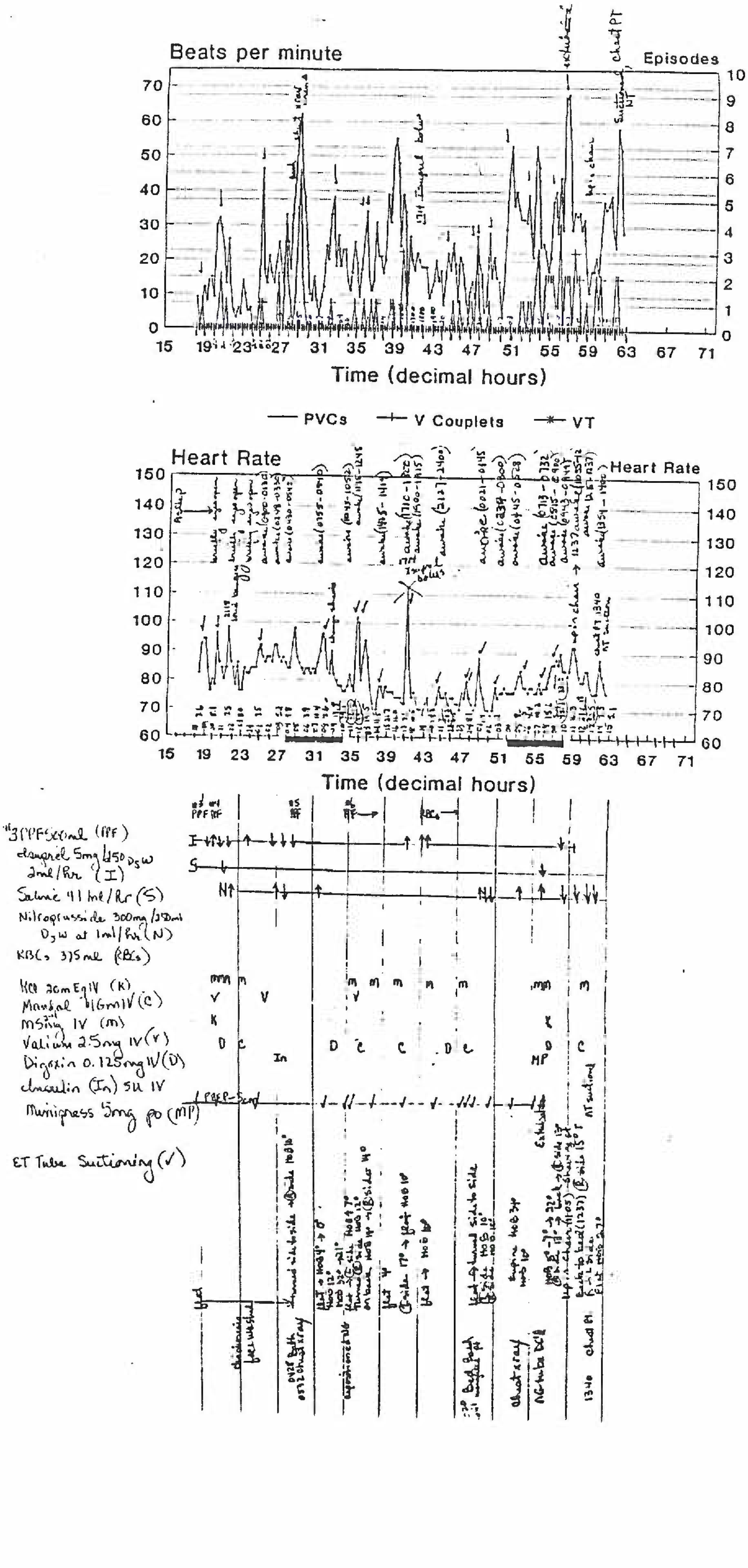
_____ _____
Surrogate Date

_____ _____
Witness Date

_____ _____
Investigator Date

Appendix K

Example of Descriptive Analysis of a Heart Rate and Rhythm Graph (Subject 6)


Beats per minute
Episodes
Time (decimal hours)
PVCs
V Couplets
VT
Heart Rate
Heart Rate
Time (decimal hours)

Abstract

Title: Temporal Patterns of Heart Rate and Rhythm, Stroke Volume, and Cardiac Output in Critically Ill Adults in a Cardiac Surgical Intensive Care Unit

Author: Su[redacted]

Approved: [redacted]
Advisor

Circadian (approximately 24 hr) rhythms in heart rate (HR) and rhythm, stroke volume (SV), and cardiac output (CO) have been found. However, few studies describing temporal patterns in these variables have included critically ill adults. It was unknown whether these variables continue to be rhythmic in critically ill postoperative, cardiac surgical patients and if so, whether the rhythms could be detected.

To describe simultaneously measured temporal pattern in HR and rhythm, SV, and CO in critically ill adults in a cardiac surgical intensive care unit (ICU), six patients aged 33-68 years, mean 48.3 $\pm$ 15.3 years, were observed continuously for 36-48 hours. HR and rhythm were measured using a Holter tape recorder. Thermodilution CO was measured every 1-4 hours; SV was derived. Treatments and environmental events were noted on the graphed variables.

Cosinor analyses of HR using whole data set and divided data set revealed 24-hour rhythms in all analyses except for one patient in the whole data analysis ($p<0.056$). Mesors, amplitudes, and acrophases differed between the two study days. Ultradian (12 hr, 6 hr, 4 hr) rhythms occurred in some subjects and differed between study days.

Cosinor analysis of arrhythmias (n=4) revealed 24-hour rhythms in PACs (n=1; p=0.004), PVCs (n=2; $p<0.062$), and ventricular couplets (n=2; p=0.001). 4-hour rhythms were found in PACs (n=1; p=0.004), atrial tachycardia (n=1; p=0.034), and PVCs (n=4; $p<0.089$). Acrophases for arrhythmias varied among individuals. Mesors, amplitudes, and acrophases differed between study days. On study day two, the 4-hour-rhythm acrophases in HR and arrhythmias were related to the timing of respiratory therapy.

SV and CO had significant 24-hour rhythms in two subjects (SV, p=0.000, 0.096; CO, p=0.006, 0.056). Mesors and amplitudes in these two subjects were similar; acrophases did not overlap.

This is the first study to describe the temporal patterns of HR and rhythm, SV, and CO simultaneously measured in critically ill adults in a cardiac surgical ICU. Knowledge that rhythms are occurring and that their characteristics are changing from day to day adds some explanatory value in understanding why changes in these variables may be seen clinically and in research settings.