The Effect of Coffee on Ventricular Arrhythmias in Cardiac Patients

by

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DEDICATION

To my loving husband, Ronald Chelsky

and my newborn baby, Zachary

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Introduction

Eighty percent of Americans consume coffee; the average amount of coffee consumed by these coffee drinkers is 3.5 cups per day (Raebel & Black, 1984). The popularity of this caffeine-containing beverage, for many people, stems from its stimulating effects and increased wakefulness (Rall, 1980). Because of the ubiquity of coffee intake and the high incidence of heart disease in the general population, the occurrence of both entities together is a common event. It is unclear to date if coffee drinking imposes an added risk to the cardiac patient. Furthermore, it is unknown if caffeine intake is safe for the patient who has a prior history of ventricular arrhythmias.

Coffee is the most common source of caffeine in the United States (Graham, 1978). Researchers have studied the effects of caffeine on the cardiovascular system for approximately 50 years. Caffeine is a cardiac stimulant that is known to decrease or increase heart rate, increase vascular blood flow and produce cardiac arrhythmias (Rall, 1980). Studies of caffeine and arrhythmias with human subjects have been very limited in numbers and they rarely involve the use of subjects with cardiac disease. The findings from these caffeine studies have often been inconsistent because the population samples and research methods have varied widely. The exact underlying mechanism by which caffeine leads to cardiac arrhythmias is as yet unclear (Mathewson, 1984).

Nursing research is more scarce than medical research in the area of caffeine ingestion and cardiac arrhythmias. Traditionally, nurses in the Critical Care Unit (CCU) restrict the intake of stimulating beverages, such as caffeinated coffee, in their cardiac patients to help prevent arrhythmias (Schneider, 1987).

To date, there is minimal nursing research to support this traditional practice. Furthermore, cardiac rehabilitation nurses also instruct their patients who have a prior history of arrhythmias to avoid caffeine ingestion. This practice, again, is not supported by research. Studies using cardiac patients as subjects are needed to examine the effects of caffeine on cardiac arrhythmias and to determine the underlying mechanism involved (Newberg, 1984).

Statement of the Problem

The aim of this study is to determine if caffeine intake, in the form of coffee, is safe for cardiac patients who have a history of ventricular arrhythmias. The question of interest is, will patients who have a prior history of ventricular arrhythmias have increased inducibility or more severe ventricular arrhythmias after ingesting caffeine in coffee form? Furthermore, will these arrhythmias that are induced by caffeine correlate with changes in plasma catecholamine or potassium levels? Elevated catecholamine plasma levels and hypokalemia or hyperkalemia can be arrhythmogenic. Are these altered blood levels associated with coffee intake and do they increase the possibility of arrhythmias?

The answer to this problem will allow health care practitioners to make a decision, supported by research, regarding caffeine intake and arrhythmias. Should caffeine intake be restricted during hospitalization in the patient who has a history of ventricular arrhythmias? Should these patients also be instructed to restrict caffeine intake after discharge from the hospital? The answer to these questions will promote patient safety and provide beneficial information for the health care practitioner regarding caffeine intake in the hospital and the cardiac rehabilitation setting. In addition, this information can be applied towards diagnosis and treatment of arrhythmias. Coffee or caffeine

products may influence electrophysiologic testing and drug therapy, and may need to be restricted prior to arrhythmia testing.

Review of Literature

The literature reviewed for the present study will include a comprehensive discussion of recent, as well as past, investigations involving the effects of caffeine on ventricular arrhythmias. Studies that discuss caffeine effects on plasma catecholamines, potassium, and calcium levels will be included. The action of these variables on myocardial fibers and the electrical conduction system will be explored. The circadian rhythm of cardiac arrhythmias will also be reviewed.

Caffeine Sources

Caffeine is found worldwide in naturally occurring plants such as coffee beans, tea leaves, kola nuts, and cocoa beans. Coffee is the most common source of caffeine that is imported into the United States. Tea and cola beverages follow coffee in popularity. Caffeine is found in other dietary substances and pharmacological products. Chocolate beverages and food items such as coffee ice cream, chocolate candy, and others contain varying amounts of caffeine (Graham, 1978). Common drugs that contain caffeine are diet pills, stimulants, analgesics, and cold remedies (Stephenson, 1977).

The various amounts of caffeine that are found in coffee, tea, cola, and cocoa are listed in Table 1. The difference in caffeine content between coffee and tea products depends on the preparation method and brewing time (Bunker, & McWilliams, 1979).

The Council on Scientific Affairs (1984) states that caffeine labeling of beverages and food items that contain caffeine is not required, because caffeine values are difficult to assign. Caffeine content per coffee serving also

Table 1

Caffeine Content in Common Beverages

Beverage	Mean caffeine mg per 100 ml
Coffee	
instant	44
percolated	73
automatic drip	97
Bagged tea	
black, 1 minute brew	20
black, 5 minute brew	33
Loose tea	
green, 5 minute brew	25
black, 5 minute brew	29
green, Japan, 5 minute brew	15
Others	
cola beverages	13
cocoa, instant	6

Bunker and McWilliams, 1979.

Table 2

Milligrams of Caffeine in a 150 ml serving of coffee

Author or source	Percolated coffee	Automatic drip coffee	Instant coffee
Council on Scientific Affairs (1984)	99-129	144.8	57-81
Food and Drug Administration (1984)	40-170	60-180	30-120
Raebel and Black (1984)	64-124 (per 5-8 oz.)	110-150 (per 5-8 oz.)	40-108 (per 5-8 oz.)
Bunker and McWilliams (1979)	97-125	137-153	61-70

varies among authors (see Table 2). Varying amounts of caffeine in products are due to the type of the raw material used, the brewing time, and preparation methods. Coffee and caffeine researchers need to be aware of these differences.

Pharmacology of Caffeine

Caffeine, along with theophylline and theobromine, is a member of the methylxanthine group (xanthine group). It is an alkaloid that is chemically structured as 1,3,7-trimethylxanthine. The three members of the xanthine group have similar pharmacological properties. In the human body, caffeine stimulates the central nervous system, produces diuresis, relaxes smooth muscles of the respiratory system, stimulates cardiac muscle, and augments release of the secretory products of several endocrine and exocrine tissues. The mechanism by which caffeine stimulates the cardiac muscle will be further discussed.

Caffeine is used to treat many conditions in adults such as: headaches, central nervous depression, atopic dermatitis, idiopathic Parkinsonism, cancer, and artificial insemination of hypokinetic sperm. A plasma caffeine level of 6-13 mcg/ml is considered therapeutic for these conditions (Facts and Comparisons, 1984). Caffeine can be administered by different routes (oral, intramuscular, intravenous, and rectal). These different routes of administration produce various absorption and peak serum times (Rall, 1980). After caffeine is ingested orally, it is rapidly absorbed, metabolized by the liver, and excreted in the urine as methylxanthine derivatives. Caffeine enters all organs and tissues within minutes after ingestion (Raebel & Black, 1984). Intake of food with caffeine slows absorption, but does not decrease the amount of caffeine absorbed (Rall, 1980). According to Facts and Comparison (1984), oral contraceptives,

cimetidine, and alcoholic liver disease will inhibit caffeine metabolism and cause increased and prolonged caffeine effects. Pregnancy causes the half-life of caffeine to be prolonged, presumably by hormonal alterations similar to contraceptives. Cigarette smoking effects the metabolism and reduces the half-life of caffeine.

Cardiovascular Effects of Caffeine

Robertson, et al. (1978) measured the effects of caffeine on the cardiovascular system of nine healthy non-coffee drinkers. On two separate days, each fasting subject drank a 300 ml beverage containing either placebo or 250 mg of caffeine. The mean blood pressure increased 14/10 mm Hg one hour after caffeine ingestion. The mean heart rate decreased from 65 to 60 beats per minute, 45 minutes after caffeine, and then increased to 70 beats per minute one hour later. This study cannot be generalized to the coffee-drinking population because its subjects were non-coffee drinkers.

Robertson, Wade, Workman, and Woosley (1981) studied the effects of caffeine on hemodynamic measures. Eighteen healthy subjects were randomly assigned to one of two treatment groups: placebo beverage for 14 days, or placebo and caffeine beverage for 14 days with caffeine given only on days four through ten. Caffeine, 250 mg, was administered in a 300 ml beverage. A mean blood pressure increase of 11.2 ± 2.5 mm Hg was significant ($p<0.01$) in subjects who consumed caffeine versus placebo. Systolic blood pressure was higher during day one and two of caffeine ingestion, and by day four systolic blood pressure returned to baseline. There was little effect on the mean heart rate after placebo or prolonged caffeine ingestion (after 7 days of caffeine ingestion).

The authors conducted an additional study using sixteen subjects who were regular coffee drinkers (average of three cups of coffee a day). Their blood pressure was measured in response to caffeine intake after abstaining from coffee for 24 hours prior to the study. Systolic blood pressure increased 2.2 ± 1.1 mm Hg in subjects who had a baseline caffeine plasma level greater than one microgram per milliliter. This was not statistically significant. A statistically significant increase in systolic blood pressure of 4.2 ± 1.3 mm Hg was noted in subjects who had a baseline caffeine level less than one microgram per milliliter. This indicates that abstinence from caffeine ingestion for greater than 24 hours is required for the maximal effect of caffeine on blood pressure to be displayed.

Izzo, Ghosal, Kwong, Freeman, and Jaenike (1983) studied the effects of age and prior caffeine use on acute caffeine induced changes of the cardiovascular system. Twenty non-smoking subjects were given 250 mg of caffeine or placebo on two separate days. These subjects were grouped into coffee (n=10) and non-coffee drinkers (n=10), and paired according to younger (<30 years) and older (>50 years) age groups. Heart rate did not vary between non-coffee drinkers and coffee drinkers. Mean arterial blood pressure was higher in older non-coffee drinkers 60 minutes after caffeine consumption. Seventy year old non-coffee drinkers had a mean arterial blood pressure that was 13% higher than coffee drinkers of the same age. Double product (heart rate multiplied by systolic blood pressure) was 20% higher in older non-coffee drinkers than in older coffee drinkers. This study demonstrates that caffeine ingestion has a greater effect on the cardiovascular system in the non-coffee drinkers, and caffeine effects are more pronounced in older subjects.

A study by Whitsett, Manion, and Christensen (1984) stated that cardiovascular effects did not differ significantly between subjects who consumed caffeine and subjects who consumed coffee. A serving of caffeine (2.2 mg/kg which equals approximately two cups of coffee) or a serving of instant coffee in an equal measured amount was given to 54 subjects after fasting and 24 hours of caffeine abstinence. These subjects were categorized according to the amount of coffee consumption and their cigarette smoking status. Blood pressure increased after caffeine and coffee ingestion (systolic increased 8.7 ± 0.99 mm Hg and diastolic increased 10.3 ± 0.78 mm Hg). Heart rate remained decreased for four hours after coffee and caffeine, 8.66 ± 0.69 and 10.7 ± 0.73 beats per minute, respectively. There were no significant differences in blood pressure and heart rate among the classification groups. Cardiovascular changes and peak plasma caffeine levels do not significantly differ between caffeine and coffee ingestion. This study offers strong evidence that the effects of coffee are related to caffeine rather some other chemical constituent of this beverage.

Summary. Acute caffeine ingestion produces an increase in systolic and diastolic blood pressure. Heart rate is unchanged or decreases after 250 mg of caffeine. The cardiovascular effects of caffeine are amplified in the non-coffee drinkers and mean arterial blood pressure increases more in older age subjects versus younger age subjects. Ingestion of coffee or caffeine produces the same cardiovascular effects in individuals.

Plasma Levels, Peak Times and Half-lives

As caffeine content per serving of coffee varies between authors (as stated earlier), so do peak plasma caffeine levels, peak times and half-lives. Facts and Comparisons (1984) reports that peak caffeine levels of 5-25 mcg/ml

are achieved within 15 to 45 minutes after ingestion of 250 mg of oral caffeine. The plasma half-life of caffeine in adults ranges from 3-7.5 hours. The average half-life is 3.5 hours.

Robertson, et al. (1978) demonstrated that plasma caffeine peaks 60 minutes after ingestion of 250 mg of caffeine to a mean plasma level of 11.6 mcg/ml ± 2.6 (S.E.M.). The plasma peak times (ranging from 30-120 minutes), and caffeine levels (ranging from 4.2-26 mcg/ml) varied among the study subjects. Identification of possible variables (body mass, cigarette smoking, medications) that could have influenced the caffeine plasma peak times and plasma levels were not stated in this study.

Robertson et al. (1981) evaluated the effects of chronic caffeine use on caffeine plasma levels and peak times. After ingestion of 250 mg of caffeine, the mean caffeine peak time was 60 minutes. Peak times ranged between 15 and 120 minutes among the subjects. The peak levels ranged from 3.8 to 14.8 mcg/ml with a mean half-life of ten hours. Peak plasma levels were 2-3 mcg/ml higher with chronic caffeine ingestion (after seven consecutive days of caffeine intake) versus acute caffeine ingestion (one day of caffeine ingestion). The elevated caffeine level occurs in chronic users because their caffeine baseline levels are initially higher. The amount of increase in plasma caffeine levels did not vary significantly between the two groups. Peak times did not differ between chronic or acute caffeine ingestion.

Izzo et al. (1983) evaluated the effects of age and prior caffeine habituation on caffeine levels and peak times. Caffeine levels peaked 60 minutes after ingestion of 250 mg of caffeine for both non-coffee drinkers and coffee drinkers. The mean caffeine level for the younger age (<30 years) group was 4.6 ± 0.5 mg/L and 5.8 ± 0.5 mg/L for the older age (>50 years) group. Age

and prior use of coffee did not influence peak caffeine times. Because caffeine levels were only measured hourly instead of every 15-30 minutes, the peak caffeine time may not have been accurately determined. The infrequent sampling favours a bias towards lower peak plasma levels.

Whitsett, et al. (1984) evaluated caffeine plasma levels and caffeine half-lives in subjects who consumed caffeine and in subjects who consumed coffee. The 54 volunteer subjects received a 2.2 mg/kg dose of caffeine or a serving of coffee that equalled 2.2 mg/kg of caffeine. Subjects were classified according to their cigarette smoking status and their prior use of coffee. Non-smoking, heavy coffee users had a shorter caffeine plasma half-life (2.53 ± 0.28 hours) than non-smoking subjects who seldom consumed coffee (3.08 ± 0.31 hours). Smokers had shorter caffeine plasma half-lives (3.21 ± 0.28 hours) than non-smokers (5.10 ± 0.5 hours). The plasma caffeine levels for both caffeine and coffee peaked at 30-60 minutes after ingestion. People who were intolerant of caffeine (because of caffeine side effects) had similar peak plasma times but prolonged half-lives (6.6 ± 1.68 hours) when compared to non-smoking, heavy coffee drinkers (3.94 ± 0.79 hours).

Summary. Caffeine half-lives, peak caffeine levels and peak times vary among individuals. Caffeine half-life is reduced when caffeine ingestion is associated with cigarette smoking and habitual use of coffee. The half-life is prolonged in naive (non-coffee) drinkers. Chronic caffeine use (everyday caffeine intake), produces plasma caffeine levels that are 2-3 mcg/ml higher than acute caffeine use. This increased level is accounted for by the elevated baseline caffeine level in the chronic coffee drinker. Peak times vary between 15 and 120 minutes.

Hormonal Effects of Caffeine

Robertson, et al. (1978) demonstrated that ingestion of 250 mg of caffeine produces an increase in plasma catecholamine levels and renin activity. Epinephrine levels increased by 207%, one hour after caffeine. Norepinephrine levels increased by 75% and plasma renin activity increased by 57%, three hours after caffeine ingestion.

Robertson, et al. (1981) studied the effects of chronic caffeine use on catecholamine levels and renin activity. Epinephrine and norepinephrine plasma levels elevated significantly ($p<0.05$) 15 minutes and 30 minutes after caffeine ingestion, respectively. These levels peaked three hours after caffeine consumption. Catecholamine levels were significantly higher ($p<0.05$) after acute (one day of caffeine ingestion) versus chronic caffeine ingestion. Plasma renin activity levels gradually increased for four hours after ingestion of caffeine. Plasma renin activity was more significantly elevated ($p<0.05$) after acute ingestion of caffeine, than with chronic ingestion (Robertson, et al., 1981).

Izzo, et al. (1983) evaluated the effects of age and prior caffeine habituation on selected hormone levels. Mean epinephrine levels steadily increased up to 180 minutes after caffeine ingestion. Norepinephrine, vasopressin, and renin activity did not change from baseline values. The lack of elevation in norepinephrine and renin activity differs from the studies done by Robertson, et al. (1978, 1981). The reason for this difference is unclear. Younger subjects had a higher epinephrine plasma level (93 ± 14 mg/L) than older subjects (79 ± 14 mg/L) 180 minutes after caffeine ingestion.

Summary. Most studies confirm that catecholamine levels and renin activity elevate after caffeine consumption. One study, however, did not report an increase in norepinephrine and renin activity after 250 mg caffeine (Izzo et

al., 1983). Catecholamine levels and renin activity increase to a lesser extent with chronic coffee use than with acute ingestion. Younger non-coffee drinkers are more sensitive to the effects of caffeine on epinephrine levels.

The Effects of Caffeine at the Cellular Level

Many researchers have linked caffeine with arrhythmogenesis, but the mechanism of these caffeine induced arrhythmias is unknown (Paspa & Vassalle, 1984). Caffeine is known to increase catecholamine levels and intracellular calcium. Extracellular potassium levels decrease as catecholamine levels elevate. These altered chemical and electrolyte levels can be potentially arrhythmogenic and will be described further. Figure 1 represents how these alterations occur and why they can potentially produce arrhythmias.

Effects of caffeine on catecholamines. Caffeine has been shown to activate the sympathetic nervous system. As Robertson, et al. (1978) demonstrated, caffeine produces elevated plasma epinephrine and norepinephrine levels one and three hours after ingestion, respectively (as previously described). This increase in catecholamine concentration reflects stimulation of the sympathoadrenal system, and primarily adrenomedullary stimulation (Robertson, et al. 1979). The concentrations of epinephrine and norepinephrine remain elevated for a longer period of time after adrenomedullary (indirect) stimulation, where as the concentrations of these chemicals are transiently elevated after neuronal sympathetic (direct) stimulation (Guyton, 1987).

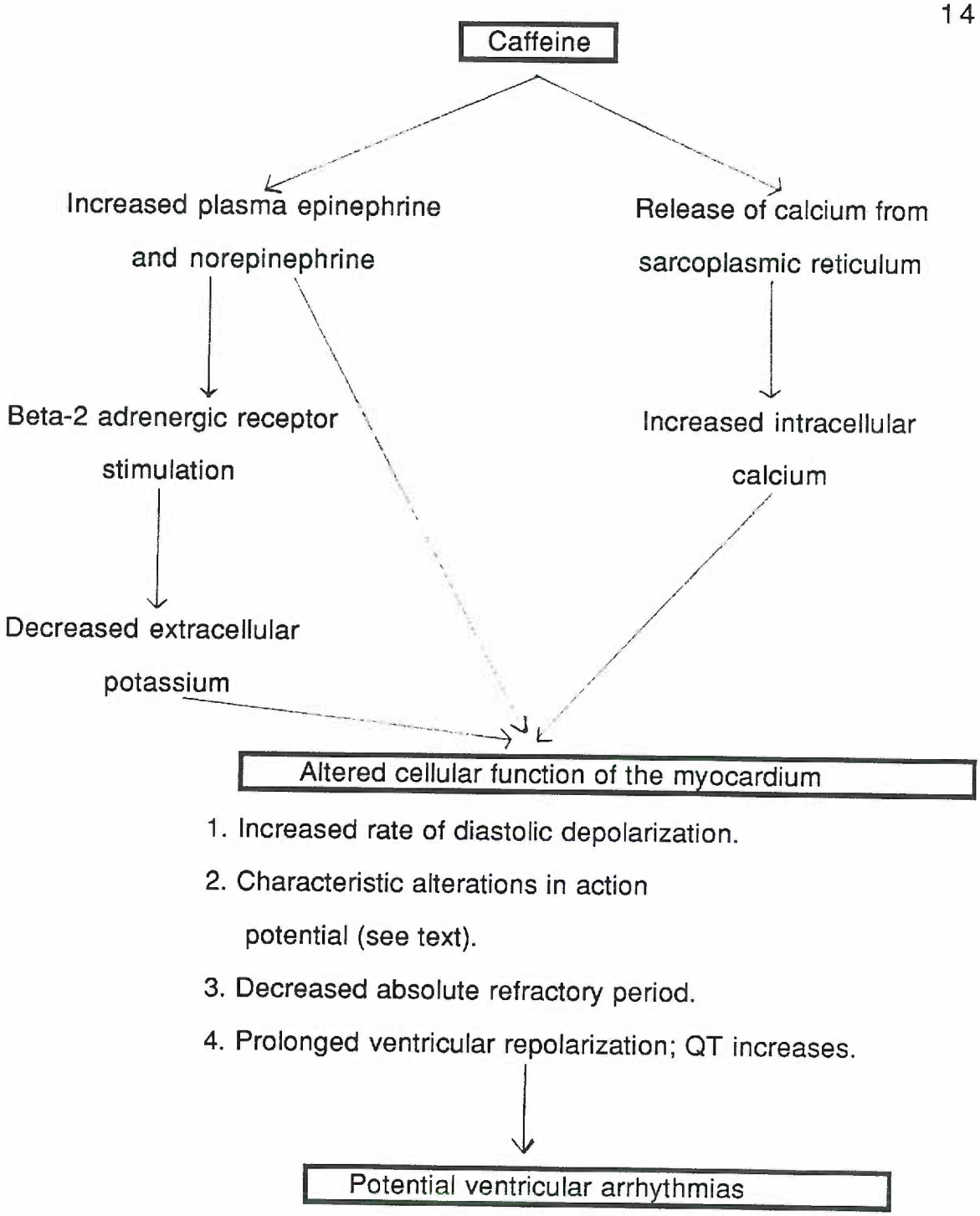

Figure 1. The cellular effects of caffeine.

Effects of catecholamines on the myocardium. At the cellular level of the target cells, caffeine prolongs or intensifies the activity of catecholamines by decreasing the rate of breakdown of cyclic adenosine monophosphate (cAMP). Cyclic AMP is formed after catecholamine, a stimulating hormone, combines with a receptor that activates adenylate cyclase, an enzyme. The active form of this enzyme converts cytoplasmic adenosine triphosphate (ATP) into cAMP (Guyton, 1987). Cyclic AMP acts as a hormonal mediator to produce specific physiological responses. Caffeine inhibits the enzyme phosphodiesterase, which breaks down cyclic AMP. Therefore, the actions of catecholamine are prolonged within the cell (Lehninger, 1982).

Sympathetic stimulation of the heart increases SA nodal discharge, increases the rate of conduction and increases the force of contraction of the myocardium. This increase in cardiac activity stems from the release of norepinephrine at the sympathetic nerve endings. This hormone also increases the permeability of the fiber membrane to sodium and calcium. Improved sodium permeability leads to an increased heart rate. An increase in calcium permeability leads to strengthening in myocardial contraction (Guyton, 1982). Sympathetic stimulation of the circulatory system causes vasoconstriction of the subcutaneous, mucosal, splanchnic, and renal vascular beds. This catecholamine stimulation is an alpha-receptor mediated mechanism (Landsberg & Young, 1983).

Struthers, Reid, Whitesmith, & Rodger (1983) studied the effects of intravenous adrenaline on electrocardiogram (EKG) intervals. Nine healthy volunteers received three consecutive 90 minute infusions of L-adrenaline (epinephrine) in five percent dextrose. The first infusion contained no adrenaline (control). The second infusion contained 0.01 mcg/kg per minute of

L-adrenaline, and the third infusion contained 0.06 mcg/kg per minute of the same. QT intervals on the EKG tracing were measured (corrected for rate) every five minutes for the first 15 minutes, then every 30 minutes after that until 120 minutes after the infusion was started. During the high dose infusion and 90 minutes after the infusion was started, T wave amplitudes decreased in eight subjects, U waves formed in three subjects, ST segments were depressed in three subjects, and QT intervals increased in eight subjects . The QT intervals (corrected for rate) increased from 0.36 ± 0.02 to 0.41 ± 0.06. The plasma adrenaline levels peaked at 5.5 ± 1.7 nmol during the high dose infusion. This study shows that elevated plasma epinephrine levels can produce changes in ventricular repolarization as demonstrated by EKG changes. These induced abnormalities of repolarization could potentially produce arrhythmias.

Morady et al. (1988) evaluated the electrophysiology effects of epinephrine infusion (25-50 pg/kg per minute) in normal (no structural defects) and diseased (CAD, cardiomyopathy) hearts. Patients with a history of sustained ventricular tachycardia were excluded. The effective refractory period of the right ventricle was significantly decreased after both infusion concentrations. One subject without heart disease, noninducible at baseline, had sustained VT after epinephrine. Two subjects with heart disease, nonsustained VT at baseline, had sustained VT after epinephrine infusion. Epinephrine at plasma concentrations of 862 ± 226 (SD) pg/ml (after 25 pg/kg per minute) and 1374 ± 477 (SD) pg/ml (after 50 pg/kg per minute) induced sustained VT in 3/20 (15%) subjects.

Factors that increase plasma catecholamines. Elevation in catecholamines is a normal response to physical and/or emotional stressors. This response is called the fight or flight reaction. During stress, the body

responds by increasing sympathetic discharge of epinephrine and norepinephrine. This prepares the body for the stressful event by augmenting cardiac function, increasing cellular metabolism, strengthening muscle function, and improving mental activity (Guyton, 1982).

Robertson, et al. (1979) demonstrated how catecholamines respond to various stimuli of the sympathetic nervous system. Plasma norepinephrine levels increase with treadmill exercise, orthostasis, caffeine ingestion, the cold pressor test, sodium restriction and the handgrip exercise. Increased norepinephrine represents sympathetic function at the nerve terminals. Plasma epinephrine levels elevate with caffeine ingestion, treadmill exercise, the cold pressor test, handgrip exercise and the Valsalva maneuver. This rise in epinephrine represents adrenomedullary discharge.

In this same study, Robertson, et al. (1979) compared blood from a heparin-lock catheter with blood by venipuncture technique. They found no significant difference in dopamine, epinephrine and norepinephrine levels between the two blood sampling techniques. A similar study by Carruthers, Conway, Taggart, Bates, and Somerville (1970) had contradictory results. They found that the epinephrine levels were significantly elevated with venipuncture when compared to heparin-lock sampling. The differences in results between the two studies could be related to venipuncture techniques. As Robertson et al. (1979) states, their venipunctures were relatively atraumatic (subjects had easily approachable veins) and this could have produced a less catecholamine response. Venipuncture can stimulate the sympathetic nervous system. To prevent elevation of catecholamine levels, blood samples should be obtained from an indwelling catheter.

Effect of catecholamines on potassium. Many researchers have correlated hypokalemia with acute serum elevation of catecholamines. Morgan and Young (1982) showed that hypokalemia occurs during stressful events, such as acute medical events. This retrospective study looked at admission plasma potassium levels in 70 patients that were less than 2.8 mmol/L. Fifty-four percent of these patients with hypokalemia had a cardiovascular event such as myocardial infarction or cerebrovascular accident. Hypokalemia in this setting was felt to be related to elevated catecholamine levels, which are commonly found in association with myocardial infarction (Karlsberg, Cryer, & Roberts 1981).

Karlsberg, et al. (1981) demonstrated that sympathoadrenal activation after myocardial infarction produces elevated epinephrine and norepinephrine levels. Fourteen patients who presented within four hours after the onset of symptoms and had elevated cardiac enzymes and EKG changes where studied. Mean epinephrine levels increased from 73 ± 19 pg/ml (S.E.M.) (initial level at onset of blood sampling) to 1098 ± 608 pg/ml (S.E.M.) (peak level during sampling) and mean norepinephrine levels increased from 591 ± 111 pg/ml to 1356 ± 178 pg/ml (S.E.M.).

Struthers et al. (1983) infused 0.06 mcg/kg per minute of L-adrenaline into nine volunteers over 90 minutes and measured the effects on serum potassium levels. Mean peak plasma epinephrine levels reached 5.5 ± 1.7 nmol/L, which is similar to the peak epinephrine levels found by Karlsberg et al. (1981) in their study of patients after acute myocardial infarction. The mean serum potassium level fell from 4.06 ± 0.14 to 3.22 ± 0.26 mmol/L and returned to baseline 90 minutes after stopping the infusion. This study demonstrates that hypokalemia

could be induced by catecholamines and suggests that hypokalemia during myocardial infarction is a result of endogenous catecholamine secretion.

Hypokalemia can be induced by an inward movement of potassium ions from the extracellular fluid into the cell. Several mechanisms exist to stimulate intracellular movement of potassium ions. One important mechanism involves catecholamine stimulation of beta 2 (ß2) receptors (Lauler, 1985). ß-receptors are widely distributed throughout the body and their stimulation leads to many end organ effects. Beta-adrenergic receptor stimulation produces an increase in heart rate, increase in contractility, vasodilation, bronchodilation, and lipolysis. Two types of ß-receptors exist with different sensitivities to the various catecholamines. Beta 1 (ß1) receptors respond equally to epinephrine and norepinephrine, and induce cardiac stimulation and lipolysis. ß2-receptors respond more to epinephrine than to norepinephrine, and stimulate vasodilation and bronchodilation (Landsberg & Young, 1983). Stimulation of ß2-receptors leads to stimulation of the sodium-potassium adenosinetriphosphatase (ATPase) system. The sodium-potassium exchange pump moves sodium ions from the interior of the cell to the extracellular fluid, while potassium ions move from the extracellular fluid into the cell (Lauler, 1985). Sodium and potassium exchange occurs by active transport. Energy used from splitting adenosine triphosphate (ATP) molecules is used to transport the ions against their concentration gradient (Guyton, 1982).

Brown, Brown, and Murphy (1983) demonstrated that epinephrine-induced hypokalemia was linked to ß2-adrenoceptor stimulation. In their first study, they infused epinephrine (0.1 mcg/kg body weight per minute) and isoproterenol (0.02 mcg /kg body weight per minute) on separate days into six normal volunteers over a 75 minute time period. Plasma epinephrine,

norepinephrine, potassium, aldosterone, insulin, glucose, and renin activity, were measured before, during and after each infusion. A fall in plasma potassium was significant within 30 minutes after the epinephrine infusion was initiated and continued for 75 minutes after the infusion was completed ($p<0.01$). Mean plasma potassium decreased from 4.15 to 3.25 meq/L ($p<0.01$). Plasma potassium increased slightly (but not significantly) during the isoproterenol infusion. Plasma aldosterone and renin activity levels did not differ between epinephrine and isoproterenol infusions. Plasma insulin increased with isoproterenol and decreased with epinephrine, and plasma glucose increased with epinephrine and not with isoproterenol. The decreased Insulin after epinephrine infusion is a result of stimulation of islet-cell alpha-adrenoceptors. This indicates that hypokalemia was not mediated by insulin, aldosterone or renin activity. The different potassium response to the two catecholamines is due to the ß1 and ß2 selectivity of epinephrine and isoproterenol. Epinephrine is primarily a ß2-receptor stimulator and isoproterenol stimulates both ß1 and ß2.

In a second study by the same authors, an experimental ß2-receptor antagonist (ICI 118551) or placebo was given one hour before infusion of epinephrine (0.05 mcg /kg per minute). Hypokalemia was not induced during epinephrine infusion after ß2-receptor blockade. Plasma epinephrine levels were similar after ß2-blockade and placebo. The fall in plasma insulin was greater after ß2-blockade than with placebo. Plasma glucose increased after placebo and ß2-blockade, but the increase was reduced after ß2-blockade. Hypokalemia, after epinephrine infusion, is a result of ß2-receptor stimulation and not influenced by glucose and insulin.

Struthers, Reid, Whitesmith and Rodger (1983) investigated the effects of placebo, atenolol (selective ß-1 blocker) and timolol (non-selective ß-blocker), on plasma potassium during epinephrine infusion. Epinephrine was infused into nine normal volunteers to reach plasma concentrations similar to those associated with myocardial infarction. The mean plasma epinephrine level without ß-blocker (placebo) reached 4.62 ± 2.4 mmol/L after a 90 minute infusion of L-adrenaline at 0.06 mcg/kg per minute. Mean serum potassium levels decreased from 4.06 to 3.22 ± 0.25 mmol/L after placebo. The serum potassium values returned to baseline within 90 minutes after the infusion was completed. Mean potassium fell from 4.06 to 3.67 mmol/L after atenolol and increased to 4.25 mmol/L after timolol. Hypokalemia was prevented with timolol (10 mg twice daily), and partially prevented with atenolol (50 mg twice daily), when given for five days prior to epinephrine infusion. There was no significant difference between the epinephrine levels during treatment with placebo, atenolol, or timolol. This indicates that ß2-blockers prevent epinephrine induced hypokalemia.

Further research by Bia, Lu, Tyler, and De Fronzo (1986) and Reid, Whyte, and Struthers (1986) supports the concept that beta adrenergic agents decrease potassium concentrations by a ß-2 receptor mechanism. Bia et al. (1986) concluded that catecholamine stimulation of ß-2 receptors produces hypokalemia. This change in plasma potassium is a direct effect and not mediated by changes in other potassium regulatory hormones. Reid et al. (1986) strongly supported that epinephrine-induced hypokalemia is a result of ß-2 stimulation. They also suggested that ß-1 receptors influence hypokalemia, but to a lesser degree than ß-2 stimulation. Smits, Hoffmann, Thien, Houben & Laar (1983) support that epinephrine and norepinephrine plasma levels do not

differ significantly after caffeine (mean plasma concentrations reached 7.8 ± 0.5 mg/ l) when given concurrently with placebo, propranolol or metoprolol.

Effects of epinephrine and hypokalemia on the myocardium. Epinephrine infusion has been shown to induce hypokalemia in healthy volunteers when levels of epinephrine similar to those seen during myocardial infarction are achieved. The EKG abnormalities seen during this infusion represent the combined effects of hypokalemia and elevated catecholamines. Hypokalemia alone produces specific EKG changes. The T waves are flattened or inverted, U waves sometimes appear, and QT intervals appear lengthened or unchanged (Myerburg, 1983). Combined effects on the EKG have also been studied by Struthers et al. (1983). QT interval (corrected for rate) lengthened from 0.36 ± 0.02 to 0.41 ± 0.06, and T wave amplitude reduced after epinephrine infusion. These EKG changes represent abnormal ventricular repolarization. The abnormalities were not noted when atenolol or timolol were given prior to epinephrine infusion. The ß-blocker prevented the direct stimulation of the myocardium as well as hypokalemia. Hence the effects contributed by hypokalemia and those from epinephrine on the EKG could not be distinguished by this method. Other studies involving potassium infusion alone have led to elucidation of hypokalemia-induced electropathophysiology. The abnormalities associated with hypokalemia are known to be conducive to arrhythmias.

Hypokalemia predispose the myocardium to arrhythmias by several mechanisms. 1) The resting potential of the cell membrane becomes more negative when extracellular potassium concentrations are reduced. 2) The rate of cardiac cell diastolic depolarization increases with hypokalemia. Diastolic depolarization, which occurs during phase four of the cardiac action potential,

initiates depolarization of pacemaker cells. When diastolic depolarization of the cardiac cells increases, then other sites may discharge faster than the sinus node (pacemaker). 3) Hypokalemia decreases the rate of repolarization; the absolute refractory period is shortened and the relative refractory period is prolonged. Decreased refractory period leads to increased ease in development of extrasystoles and reentrant arrhythmias. 4) Conduction velocity of the myocardium is decreased, especially in the atrioventricular node (Felver, 1989).

Summary. Caffeine ingestion stimulates the sympathoadrenal system to produce elevated plasma catecholamine levels. Excess plasma epinephrine stimulates ß2-receptors and drives potassium ions into the cells. It is likely that caffeine consumption produces hypokalemia through this mechanism. A small change in extracellular potassium has a major influence on myocardium cells. Hypokalemia is known to predispose the myocardium to arrhythmias, especially diseased myocardium. Because of this mechanism, caffeine intake can be potentially harmful to persons with diseased myocardium.

Effects of caffeine on calcium. Caffeine produces increased cellular levels of calcium in the myocardial cells by enhancing the effects of catecholamines at the cellular level. As described earlier, caffeine prolongs or intensifies the activity of catecholamines by inhibiting the enzyme phosphodiesterase and hence decreasing the rate of cAMP break down. Increased cyclic AMP improves the rate of calcium ion release into the cytosol from the sarcoplasmic reticulum (SR) and augments calcium influx by opening the slow channels of cell membranes (Braunwald, Sonnenblick, & Ross, 1980). Caffeine also inhibits calcium efflux into the extracellular space. Through this integrated mechanism caffeine produces a high intracellular concentration of

calcium allowing for the manifestation of specific physiologic effects including increased contractility and increased rate of relaxation (Di Gennaro & Vassalle, 1984).

Effects of caffeine and calcium on the myocardium. Caffeine exerts a dose dependent effect on the function of myocardial fibers by inducing certain electrical and mechanical alterations. Caffeine ingestion acts at the cellular level by increasing intracellular calcium. This increase affects the cardiac action potential and increases the contractile force of the myocardium cells (Di Gennaro & Vassalle, 1985).

Di Gennaro and Vassalle (1984) studied the effects of caffeine on the role of calcium in small trabeculae carneae or papillary muscles of mongrel dogs. These tissues were tested under various caffeine and calcium concentrations. Caffeine (dose dependent) induced larger and longer twitches as a result of increased contractile force. Relaxation rates after twitches decreased with caffeine. Caffeine induces a contracture force even in the absence of extracellular calcium. The authors believed the increased force results from caffeine induced calcium release from the SR. Additionally, reduced relaxation rate is thought to be linked to slow uptake of calcium in the SR. This allows calcium to function longer at the myofilaments.

In the presence of caffeine, the plateau phase of the cardiac action potential shifts to a more positive value and the slow response increases. In the absence of extracellular calcium, the plateau shifts to a more negative value. Phase three (final rapid repolarization) and recovery of the action potential during diastole is slowed by caffeine stimulation. These alterations are most likely related to slow uptake of calcium by the SR. These changes may predispose the myocardium to arrhythmias.

Paspa and Vassalle (1984) studied the mechanism of caffeine induced arrhythmias in canine purkinje fibers. Caffeine was introduced to prepared purkinje fibers at various concentrations and action potential and muscle twitch responses were measured. Caffeine was shown to induce an oscillatory potential (V_{os}) superimposed on early diastolic depolarization in driven (stimulated) fibers. The magnitude of V_{os} increased with both caffeine dose (high concentrations) and time of caffeine exposure. It was further noted that V_{os} could attain threshold and initiate spontaneous repetitive activity if the drive was interrupted. It was concluded that spontaneous firing induced by V_{os} can induce arrhythmias. When caffeine was tested with high levels of calcium, V_{os} was more pronounced than with caffeine alone. The addition of norepinephrine to caffeine led to fast peaking of V_{os} and the initiation of fast spontaneous rhythms. These data indicate that caffeine causes an oscillatory potential that can induce arrhythmias, that this is most likely mediated by intracellular calcium and is shown to be enhanced by norepinephrine stimulation.

Summary. Caffeine induces an increase in intracellular calcium by increasing levels of cAMP. Through this mediator calcium influx is enhanced by 4 mechanisms: 1) opening the slow channels of cell membranes to increase calcium influx; 2) decreasing calcium efflux from cells; 3) increasing calcium release from the SR; 4) preventing the reuptake of calcium by SR. Increased intracellular calcium leads to increased contractile force as well as many specific changes in the characteristics of the action potential discussed above. Of major importance is the finding that in purkinje fibers a dose dependent caffeine induced oscillatory potential (V_{os}) may initiate spontaneous repetitive activity. This spontaneous firing induced by V_{os} increases the likehood of arrhythmogenesis.

Caffeine and Arrhythmias

The study of caffeine and its ability to induce or not induce arrhythmias has been explored by many researchers, predominantly medical researchers. Caffeine has been studied in both man and animals. A majority of studies have been done with healthy human subjects. Some studies have included subjects with heart disease (myocardial infarction, cardiomyopathy, mitral-valve-prolapse syndrome, others).

Bellet, Horstmann, Roman, and DeGuzman (1972) studied the effect of caffeine on the ventricular fibrillation threshold (VFT) in normal dogs and in dogs with experimentally induced myocardial infarction. These anesthetized dogs were either given caffeine sodium benzoate (25 mg/kg body weight) or sodium benzoate (12.5 mg/kg body weight) (control). The effects of caffeine on arrhythmias were measured by two different methods: VFT was determined in dogs by delivering electrical impulses through the chest wall (Group A); or by delivering impulses to the heart through implanted epicardial electrodes (Group B). The VFT significantly decreased in normal dogs after caffeine injection during both study methods ($p<0.001$). There was also a significant decrease in VFT four days after myocardial infarction with caffeine injection ($p<0.01$). Later in the study, propranolol (0.2 mg/kg body weight) was administered with caffeine in nine normal dogs and propranolol alone was given to five normal dogs (control) in group A. Practolol (0.6 mg/kg body weight) was given with caffeine in five dogs in group B. The VFT did not decrease when propranolol and practolol were administered with caffeine.

In summary, this study shows a strong correlation between caffeine and a decreased threshold for ventricular arrhythmias. Beta blockers inhibited arrhythmias in these dogs after caffeine administration. The results from this

study cannot be generalized to the human population because the caffeine doses used in this study may not be equal to a normal dose of caffeine for man. Also, the arrhythmia mechanism in dogs may be different for man.

Prineas, Jocobs, Crow and Blackburn (1980) found a positive association between coffee and tea consumption and the presence of premature ventricular beats (PVB) in man. Data were collected from 7252 healthy subjects with a coffee and tea questionnaire and a two minute rest electrocardiogram (EKG) recording. Increased occurrence of PVB was significantly correlated with large amounts of caffeine intake (up to nine cups per day).

This study is limited by the lack of plasma levels to measure actual caffeine ingestion. A self-report questionnaire may have reported biased and inaccurate amounts of caffeine (tea, coffee) intake. A two minute rest EKG is a limited measure of ectopic beats. The variability of this two minute measurement is great. In order to get a true measure of VPB related to caffeine, an EKG tracing needs to be done near the peak caffeine plasma time and over a longer time period.

Newburg (1984) studied the effects of caffeinated coffee (150 ml) and decaffeinated coffee in 20 healthy subjects. A baseline EKG was obtained prior to the study, and 30 minutes and 60 minutes after consumption. A questionnaire related to daily caffeine intake was completed. No significant difference in ectopy was noted between the two groups. There was no correlation between average daily caffeine intake and occurrence of ectopy after caffeine consumption.

The limitations of this study are similar to the study by Prineas, et al. (1980). There were no plasma caffeine levels measured, and the questionnaire results may be biased. The results from this study are adversely influenced by

the minimal amount of caffeine that was administered. A 150 ml serving of coffee may equal 30-153 mg of caffeine. The amount of milligrams used in this study is not stated.

Schneider (1987) studied the arrhythmogenic effects of caffeine in the acute myocardial infarction (AMI) population. The effects of caffeine on arrhythmias, in relation to daily caffeine use, was analyzed. Habitual caffeine consumption was categorized by daily intake levels: low (<49 mg), intermediate (50-499 mg), and high (≥500 mg). Twenty male, hemodynamically stable subjects, approximately three to ten days post AMI were chosen. Each subject acted as his/her own control and was given 150 ml of decaffeinated coffee or 150 ml of caffeinated coffee 24 hours apart. The subjects fasted four hours prior to each testing period. Testing occurred between 3:30 and 4:00 P.M. The investigator monitored the arrhythmias from a bedside oscilloscope 30 minutes prior to beverage ingestion and for a 90 minute period after beverage ingestion. A self-report questionnaire of daily caffeine consumption was completed by each subject. There was no significant difference in the cardiac rhythms during baseline and caffeine and decaffeinated ingestion periods. There was no significant difference in cardiac rhythms between low, intermediate, and high caffeine consumers. The authors suggest that one cup of caffeine may be safely given to the AMI patient, after a social and medical history is obtained, while being closely monitored in the CCU environment. Each patient needs to be individually evaluated.

This study did not scientifically determine the milligram contents of the caffeinated beverage. A 150 ml serving of caffeinated coffee may have been a low dose of caffeine. All the subjects were receiving cardiac medications (antiarrhythmics, antianginals, antihypertensive, diuretics) during the study

period, which may have masked the effects of caffeine on the cardiac rhythms. Seventy percent of the subjects were habitual caffeine users, ie., consumed greater than 49 mg of caffeine per day. These subjects may have developed a tolerance to caffeine. Abstinence of caffeine and cigarette smoking prior to the study was not discussed.

Sutherland, McPherson, Renton, Spencer, and Montague (1985) studied the effects of caffeine in 18 normal subjects (Group 1) and in 18 subjects with a prior history of frequent ventricular ectopic beats (Group 2). The subjects abstained from caffeine for 72 hours. A Holter monitor recording was done during the last 24 hours of the caffeine abstinence period. During the control and test period, patients were encouraged to continue their normal work, play and sleep activities. Servings of 180 ml of instant coffee containing one milligram per kilogram of body weight of caffeine were administered to each subject at intervals of one half-life during waking hours. During the period of caffeine ingestion, a 24 hour Holter monitor recording was again obtained. Each subject consumed servings of coffee during the waking hours to maintain a serum caffeine level greater than 2 mcg/ml. Frequency of coffee servings were determined by individual caffeine half-lives.

Heart rate did not significantly differ between groups or between caffeine abstinence and caffeine ingestion. The occurrence of PVB in Group 1 did not significantly increase with caffeine ingestion. In Group 2, the mean frequency of PVB increased from 207 $\pm$ 350 PVB per hour in the baseline period to 307 $\pm$ 414 PVB per hour during caffeine consumption ($p<0.01$). The QT measurement on the EKG did not differ significantly between the caffeine free period and the caffeine period in Group 1 or 2. The increase in PVB during the caffeine period was present only during the waking hours and not the sleeping hours. The

authors suggest that caffeine should be used with caution in patients who are at increased risk for ventricular arrhythmias.

The difference in frequency of PVBs between caffeine abstinence and caffeine ingestion was significant in group 2. This difference was significant despite the low plasma caffeine levels that were maintained during the caffeine period. The study was strengthened by the maintenance of a constant plasma caffeine level that was predetermined for each individual. This study does not differentiate between naive and chronic coffee drinkers. The subjects in Group 2 need to be described further, so that a link between cardiac disease and increased PVB can be determined. Individual circadian rhythms were not discussed.

Follow-up research was conducted by Newcombe, Renton, Rautaharju, Spencer and Montague (1988) to exclude the possibility of a beta-error in the research results for normal subjects from Sutherland et al. (1985). Sample size and milligrams of caffeine were increased to reduce the error of not rejecting the null hypothesis in the normal population. Thirty-four normal adults with no evidence of cardiac disease were recruited for the study. The protocol was identical to Sutherland et al. (1985) except coffee doses were given at intervals of every 0.5 half-life during the waking hours over a 24 hour time period. Final average serum caffeine concentrations for the study population were 3-7 mcg/ml. The mean heart rate did not significantly increase (75 ± 9 -73 ± 11 bpm). The incidence of ventricular or supraventricular ectopic arrhythmias did not significantly increase between the control and the study group. The results from this study are in agreement with the results from Sutherland et al. (1985). Newcombe et al. (1988) state that heart rate and arrhythmias do not statistically

or clinically increase in normal subjects with moderate or high doses of caffeine. Weakness and strengths for this study are the same as Sutherland et al (1985).

Myers, Harris, Leenen, and Grant (1987) studied the effects of caffeine on ventricular arrhythmias in 70 subjects 7 ± 1 days (S.E.M.) post myocardial infarction. Each subject, after a light breakfast, was given a placebo beverage or 250 ml of decaffeinated coffee with 300 mg of caffeine, on two separate days. Heart rhythms were monitored for four hours with Holter monitoring, and plasma caffeine and catecholamine levels were measured hourly during this time period. The frequency and the severity of ventricular arrhythmias did not increase after caffeine ingestion. PVB occurred in the same subjects regardless of placebo or caffeine ingestion. Atrial arrhythmias (atrial premature complexes, paroxysmal atrial fibrillation, supraventricular tachycardia) were uncommon, but did occur in three subjects after both placebo and caffeine. Plasma caffeine levels peaked one hour after ingestion to a level of 5.2 ± 0.2 mg/L (S.E.M.). Epinephrine levels peaked three hours after caffeine, from 58 ± 4 pg/ml to a maximum of 88 ± 6.0 pg/ml (S.E.M.). The elevation of epinephrine levels was not influenced by concurrent beta blocker therapy in some patients. The authors concluded that this population of subjects can ingest moderate amounts of caffeine without risking development of serious ventricular arrhythmias.

The strength of this study is its double blind design. But the study is weakened by a lack of control over drug therapy (beta blockers) during the time of caffeine ingestion, short Holter monitoring periods and no description of activity patterns during the testing period. The reproducibility of Holter monitoring is poor unless at least 48 hours are obtained. Sixty-eight of the 70 subjects were chronic coffee drinkers and consumed an average of six cups of

coffee or tea a day. The habitual coffee drinkers may have skewed the study results. Abstinence from caffeine and smoking prior to the study was not stated.

A follow up study by Myers and Harris (1988) using 300 to 450 mg of caffeine in 105 patients (seven days post myocardial infarction) supported that caffeine did not cause any increase in the frequency or severity of ventricular arrhythmias. This study used the same design as described above, except an extra 150 mg of caffeine was given to 35 of the 105 patients after the initial 300 mg of caffeine and four hours of Holter monitoring. In one patient six beats of VT occurred after 450 mg of caffeine. This was the worst ventricular arrhythmia developed with the higher caffeine dose. Strengths and weakness related to this study are similar to the previous study.

Harris et al. (1989) evaluated ventricular arrhythmias associated with caffeine (450-900 mg/day) in 24 subjects with a history of organic heart disease. Subjects with a history of sustained VT or recent myocardial infarction were excluded. The group had a mean age of 58 years, 16 males and 8 females, and a mean left ventricular ejection fraction of 44%. A double-blind placebo controlled design was implemented and frequency and severity of arrhythmias were monitored with ambulatory electrocardiographic recording (24-48 hours). A caffeine-free diet was maintained for 48 hours prior to ingestion of pill form caffeine. Caffeine levels peaked from 6.2 to 9.4 mg/L depending on doses given. Ventricular premature beats per hour, pairs of VPB/day, and VT runs/day increased after 450 and 900 mg of caffeine when compared to placebo. All patients at baseline with VT continued to have VT on caffeine. Ten out of 14 patients (71%) with no VT at baseline had VT after caffeine. Patients with low ejection fraction (34-48%) were more susceptible to VT after caffeine. These

researchers concluded that caffeine should be avoided in patients with organic heart disease because of its proarrhythmic effect.

Double-blind design, selected patient population, and amount of caffeine used strengthen this study. Ambulatory EKG monitory does not measure the inducibility of sustained VT. The reproducibility of this method is more valid with at least 48 hours of monitoring. Description of activity periods were not defined. This abstract has an unclear definition of VT. It is assumed that these patients had nonsustained VT measured before and after caffeine because all sustained VT patients were excluded from the study. It is also unclear if the patients had VT after 450 mg or after 900 mg of caffeine. Pill form of caffeine does not represent a true relationship between ventricular arrhythmias and coffee.

Dobmeyer, Stine, Leier, Greenberg, and Schaal (1983) studied the electrophysiologic effects of caffeine and the arrhythmogenic potential of caffeine in seven normal volunteers and 12 patients with heart disease (mitral-valve-prolapse syndrome, cardiomyopathy, syncope history, palpitation history). Each subject had a caffeine history of three to five cups of coffee per day. All antiarrhythmic drugs were stopped 24 hours prior to the study and regular caffeine consumption was held 48 hours prior to the study. Patients one through five received 200 ml of coffee containing 200 mg of caffeine. Patients six through twelve and the normal volunteers received 200 mg of caffeine citrate intravenously. Electrophysiologic studies were performed before caffeine and ten minutes after intravenous caffeine or 30 minutes after oral caffeine. Programmed atrial and ventricular pacing were accomplished with pacing catheters positioned at the mid left atrium, the high and low lateral right atrium, the coronary sinus, the His bundle, and the right ventricular apex.

Maximum serum caffeine concentrations after caffeine citrate were 5.3 ± 1.7 mcg/ml ten minutes after infusion. Oral caffeine peaked serum levels to 3.2 ± 0.4 mcg/ml, 30 minutes after ingestion. Caffeine did not significantly change conduction intervals or sinus-node recovery times. The effective refractory period of the high and low right atrium, the atrioventricular node ($p<0.01$), and the right ventricle ($p<0.02$) were significantly shortened. The effective refractory period of the left atrium was increased ($p<0.02$). Two patients had nonsustained ventricular tachycardia during programmed ventricular pacing after caffeine intake. Three of the normal subjects had sustained atrial flutter-fibrillation during atrial stimulation after caffeine infusion. One patient had sustained atrial tachycardia before caffeine and six patients had sustained atrial flutter-fibrillation after receiving caffeine. One patient had sustained atrioventricular nodal-reentry tachycardia after receiving caffeine. In conclusion, ventricular arrhythmias were noted only in the patient group after caffeine. Supraventricular tachycardia was noted in both the patient and normal volunteer groups after caffeine. The authors of this study suggest that caffeine consumption should be avoided in patients who have had arrhythmia symptoms associated with caffeine intake. In general, caffeine induced arrhythmias occur in a spontaneous fashion, and caution should be implemented.

This study is weakened by the small sample size. The electrophysiology protocol used only up to two extrastimuli. This shortened protocol may have missed subjects who possibly could be induced with three or four extrastimuli. The researcher does not state if the patients had a history of documented arrhythmias prior to the study. Baseline electrophysiology results are not given. Correlation of individual caffeine levels with arrhythmias may have been helpful

to determine if high caffeine levels produced more of an arrhythmogenic effect on atrial or ventricular arrhythmias.

Summary. The previous research studies have demonstrated conflicting results with regard to caffeine and arrhythmias. Some studies showed that there was no relationship between caffeine and arrhythmias, and others demonstrated that caffeine reduced the ventricular fibrillation threshold, increased or showed no change in the occurrence of PVBs, or produced atrial and ventricular tachycardias. These inconsistent results could be related to the method used for measuring the arrhythmias, the amount of coffee or caffeine that was administered, or the subjects comprising the samples. The effects of caffeine were measured by a two minute EKG tracing, a bedside oscilloscope, 4-48 hour Holter monitor, and an electrophysiology study. Caffeine doses ranged from 150 ml of coffee to 900 mg of caffeine. The subjects selected for the studies were either volunteers or patients with or without a history of ventricular arrhythmias. Some studies did not control for extraneous variables, such as a prior history of caffeine ingestion, cigarette smoking, age, body mass, drugs, and underlying diseases. The results from some studies were strengthened by measurements of caffeine and catecholamine levels and other studies lacked these measurements. Peak caffeine levels and peak times are known to vary between individuals. These variation were controlled for in the study by Sutherland, et al. (1985) by pre-determining individual caffeine half-lives. In most studies the time of day the study was conducted was not stated, and individual circadian rhythms were not assessed. Cardiac arrhythmias may be influenced by circadian rhythms.

Circadian Variation of Ventricular Arrhythmias

The circadian pattern of ventricular ectopy and sudden death in ambulatory cardiac patients (excluding acute myocardial infarction) will be reviewed here. Factors that may be responsible for circadian variation of ventricular arrhythmias may be the degree of sleep (sleep stage), degree of exercise, autonomic tone (sympathetic or parasympathetic tone), circulating catecholamines, and hemodynamics (Yanaga et al., 1982). The review of this phenomenon will address circadian rhythms in relation to arrhythmia interpretation by electrophysiology testing.

Ventricular ectopy. Lown, Tykocinski, Garfein and Brooks (1973) studied 31 ambulatory patients with coronary artery disease with continuous 24 hour EKG monitoring (960 hours). There was a significant decrease in the frequency and severity of PVBs during sleep.

Yanaga et al. (1982) evaluated the diurnal variation of PVBs in 16 cardiac patients (with various day-night patterns) by continuous Holter monitoring. They noted that increased frequency of PVBs occurred during the waking hours (6AM-6PM) for individuals with day patterns. Patients who slept during the day hours had more PVBs during the night. This study supports that circadian variation exist with ventricular arrhythmias, and this variation correlates with individual day-night lifestyles.

Orth-Gomer et al. (1982) noted that the frequency of PVBs increased significantly during the day hours (6 AM to 6 PM) in patients with ischemic heart disease. These patients all had day awake and night sleep patterns. Measurements were done with 24 hour electrocardiogram monitoring during activities of day-time work and night-time rest.

Nademanee, Olukotun, Robertson, Harwood & Singh (1989) studied the circadian variation of PVBs and VT in 33 patients with malignant VT by Holter monitoring. They found a significant correlation (r=.67) between increased frequency of PVBs and time of day (1 PM and 6 PM). Episodes of VT were significantly elevated during these hours also. These researchers attributed this increase in arrhythmias to diurinal variation of sympathetic activity since beta-blockers, when given to these same patients, suppressed the arrhythmias during further monitoring. Individual day and night activities of these patients were not discussed.

Sudden Cardiac Death. Muller et al. (1987) did a retrospective study to ascertain whether there was a circadian variation in the occurrence of sudden cardiac death. Death certificates of 2203 individuals were examined for time of death in relation to sudden cardiac death. A statistically significant ($p<0.01$) circadian pattern was discovered for out-of-hospital sudden death events. There was an increased frequency of sudden deaths that occurred between 7 and 11 AM and a low frequency of deaths that occurred during the night. The occurrence of in-hospital sudden cardiac deaths were sporadic over a 24 hour period. The lack of a circadian pattern for in-hospital sudden death events could be a result of chaotic day/night activities and a lack of circadian patterns in these individuals. The use of death certificates is not a good measurement of actual time or cause of death for out-of-hospital events, because many deaths are unwitnessed. The actual time of death may be inaccurate. This study did not screen for deaths due to ischemia versus electrical instability. It was not possible for the investigators of this study to identify individual day-night patterns of activity.

The Framingham Heart study population was used to determine if circadian variation of sudden cardiac death due to electrical instability existed (Willich et al., 1987). Time of death was determined by witness interview, medical and autopsy reports, newspaper accounts of the death, or death certificates. Patients who were hospitalized or bedridden were excluded from the study. Data from 429 deaths demonstrated a peak incidence of sudden cardiac deaths between the hours of 7-9AM. There were less deaths during normal hours of sleep (11PM-6AM) than during active awake hours. The decreased frequency of sudden cardiac deaths during the sleeping hours could be a reflection of less witnesses during that time period. This study did not screen for day-night patterns of the individuals they studied.

Electrophysiology testing. Cinca, Moya, Figueras, Roma & Rius (1986) evaluated 12 patients who had recurrent episodes of supraventricular tachycardia with electrophysiology measurements. Recording of the measurements were done every one to two hours during a 24 hour period except between 3 AM and 7PM. In relation to ventricular arrhythmias, the QT interval and the right ventricular effective refractory period (ERP) showed slight daily variations. Significant prolongation of the QT interval was seen from 10PM to 9AM and significant lengthening of the right ventricular ERP was seen between 2AM to 3AM. All electrophysiologic parameters, except atrium-ventricular conduction intervals, showed circadian variations with an acrophase between 12AM and 9AM. Reasons for these changes were thought to be related to circadian variation of the autonomic nervous system. Individual circadian patterns were not discussed.

A further research study by Cinca, Moya, Bardaji, Figueras and Rius (1987) analyzed daily variation in induction of reciprocating atrial tachycardias.

They repeated bedside electrophysiologic measurements every one to two hours in 13 patients with left-sided Kent bundles and recurrent supraventricular tachycardia during a 24 hour time period (except during 3AM to 7AM). The ability to induce tachycardia with electrical stimulation from the coronary sinus and the right ventricular was highest between 1PM and 2PM. Frequency of inducibility was lowest between 12 AM and 7 AM and associated with a significant prolongation of the RR interval, retrograde Kent ERP, atrial ERP, and right ventricular ERP. Again, circadian variations in the autonomic nervous system were thought to be responsible for the changes in RR interval and refractory periods. The results indicate that there exists a nocturnal protection against electrical induction of reciprocating tachycardia that is associated with prolonged refractory periods. Individual circadian patterns were not discussed.

McClelland, et al. (1989) performed a retrospective study of ventricular electrical instability in relation to circadian patterns. A group of 231 patients with a known history of ventricular arrhythmias underwent two ventricular stimulation studies at various times of the day, four to 24 hours apart. The electrophysiology protocol used by these researchers is the same protocol used for this current caffeine study. In their findings, they concluded that there were no significant difference between the first test and second test in relation to duration of induced arrhythmia, frequency of induction of sustained ventricular tachycardia (VT), number of extrastimuli required for induction of VT, or rate of induced VT despite time of testing during the day. Individual circadian patterns were not evaluated.

Minimal research data is available regarding circadian variations of electrophysiologic measurements, especially programmed ventricular stimulation. These three studies are weakened by lack of identification of day

and night activities of the individual subjects. It may be assumed by the reader that these subjects followed a day-wake and night-rest pattern because these electrophysiology evaluations were done in a hospital setting (which requires a day-wake and night-rest pattern).

Summary. Most researchers conclude that the occurrence of ventricular ectopy is more pronounced during the waking hours than during sleeping hours in ambulatory cardiac patients. These researchers used EKG and Holter monitors to make this conclusion. The increased occurrence of sudden death events were also strongly correlated with an early morning and day time pattern. This type of measurement is flawed because of the lack of death witnesses. More research needs to be done in the area of electrophysiological testing, especially programmed ventricular stimulation. Cinca et al. (1986, 1987) concluded that QT intervals and ERP measurements become prolonged during sleeping hours. This supports that ventricular arrhythmias are less likely to occur during these hours.

The value of circadian variation of ventricular arrhythmias is important with diagnosing and pharmacological treatment of these arrhythmias. Also, researchers using electrophysiology as measurement tool need to control for time as an influencing variable. This is important when subjects have a night pattern lifestyle and sleep during the day. These individuals may have less frequent or less severe arrhythmias during the day (their usual sleep period) than during the night (their usual activity period).

Conceptual Framework

Coffee is an everyday beverage that is enjoyed by many people, but unfortunately it may be harmful for some individuals who have heart disease.

Figure 2 is a conceptual framework model that describes how caffeine, a chemical that is found in coffee, may or may not be arrhythmogenic in certain individuals.

The cardiac patient who has a prior history of ventricular arrhythmias (nonsustained, sustained ventricular tachycardia or ventricular fibrillation) is at increased risk for further arrhythmias. Most of these patients undergo medical or surgical management in attempt to ablate these potentially life threatening arrhythmias (Baroldi, 1986).

Cardiac arrhythmias in individuals with heart disease can be initiated by a stimulating substance such as coffee. As a stimulating agent, it is known to increase plasma catecholamine levels (Robertson et al., 1978). After caffeine ingestion, an increase in catecholamine levels and intracellular calcium can cause alteration of the myocardium that may lead to arrhythmias (Di Gennaro, & Vassalle, 1985). Hypokalemia, a phenomenon that occurs as a result of high plasma catecholamine levels, can also alter the electrical and mechanical function of the myocardium (Struthers et al., 1983, 1983, Felver, 1989).

Caffeine, a cardiac stimulant, is found in many other sources besides coffee. Coffee happens to be the most popular source of caffeine in traditional American and European diets. Caffeine can also be found in other beverages, food items, prescription drugs and over-the-counter drugs (Graham, 1978). Caffeine ingestion, by the patient who has had previous ventricular arrhythmias, may produce further arrhythmias.

Electrophysiology testing is a method that is presently used to diagnose and treat supraventricular and ventricular arrhythmias (Levy, 1984). This method will measure the arrhythmogenic effects of caffeine in patients who are prone to arrhythmias. Caffeine may or may not make this patient

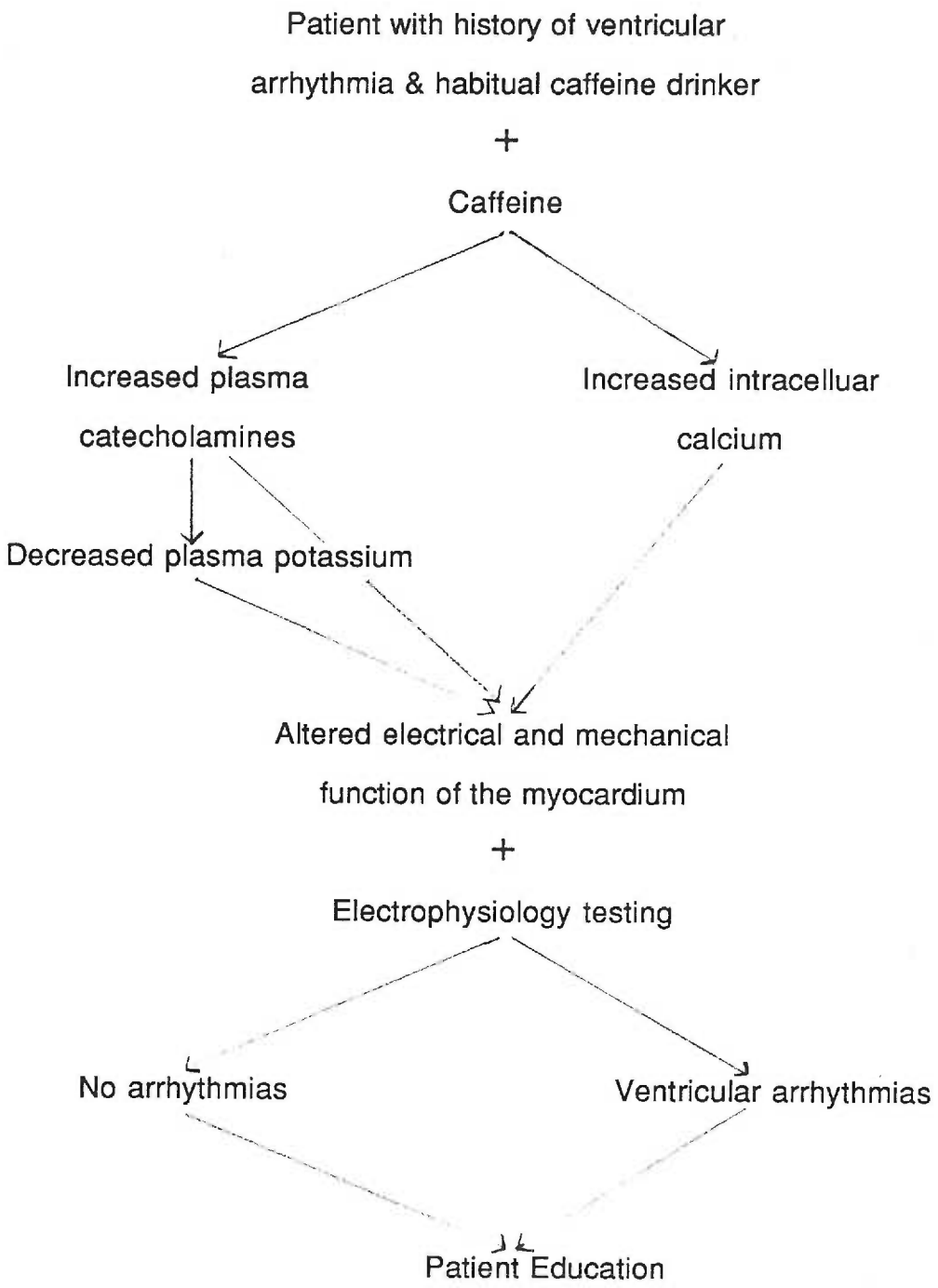

Figure 2. Conceptual framework model describing the relationship between caffeine ingestion and ventricular arrhythmias in cardiac patients.

population susceptible to ventricular arrhythmias. Patient education about caffeine ingestion is necessary due to the potential arrhythmogenesis of this dietary product.

Research Hypotheses

The hypotheses for this study stem from observing the clinical setting and reviewing the literature in this subject area.

1. Cardiac patients who have a prior history of ventricular arrhythmias will have more severe arrhythmias during electrophysiologic testing one hour after ingestion of 275 mg of caffeine (in coffee form) than during a caffeine-free (baseline electrophysiologic) test (see Appendix A for severity classifications).

2. Cardiac patients who have a prior history of ventricular arrhythmias will have more easily induced arrhythmias during electrophysiologic testing one hour after ingestion of 275 mg of caffeine (in coffee form) than during a caffeine-free (baseline electrophysiologic) test (see Appendix A for inducibility classifications).

3. In cardiac patients who have a history of ventricular arrhythmias, increases in plasma catecholamine levels will be positively correlated with the severity of arrhythmias (see Appendix A) during electrophysiologic testing one hour after ingestion of 275 mg of caffeine in coffee form.

4. In cardiac patients who have a history of ventricular arrhythmias, increases in plasma catecholamine levels will be positively correlated with the inducibility of arrhythmias (see Appendix A) during electrophysiologic testing one hour after ingestion of 275 mg of caffeine in coffee form.

5. In cardiac patients who have a history of ventricular arrhythmias, decreases in plasma potassium levels will be positively correlated with the severity of arrhythmias (see Appendix A) during electrophysiologic testing one hour after ingestion of 275 mg of caffeine in coffee form.

6. In cardiac patients who have a history of ventricular arrhythmias, decreases in plasma potassium levels will be positively correlated with the inducibility of arrhythmias (see Appendix A) during electrophysiologic testing one hour after ingestion of 275 mg of caffeine in coffee form.

Definition of Terms

Cardiac patients who have a history of ventricular arrhythmias. Cardiac patients who have a history of ventricular arrhythmias are patients who have previously experienced and survived an episode of ventricular tachycardia or fibrillation (not related to coffee drinking). A person with a history of ventricular arrhythmias is defined as someone who has experienced an episode of non-sustained or sustained ventricular tachycardia or fibrillation in the past. Death caused by ventricular arrhythmias can be impeded by cessation of the ventricular arrhythmia with quick medical interventions (Baroldi, 1986). Individuals with acute or chronic cardiac disease are eligible for this study. Cardiac diseases that may cause arrhythmias are: congenital malformations, myocarditis, cardiomyopathy, atherosclerotic heart disease, thomboembolic events, valvular disease, heart tumors and diseases of the conduction system (Wolff-Parkinson-White syndrome). The patients selected for this study are habitual coffee drinkers that have an underlying cardiac disease.

Habitual caffeine consumer. For this study the habitual or chronic caffeine consumer is defined as a individual who drinks coffee or other caffeine beverages regularly on a weekly basis. These individuals do not state that they

are sensitive to caffeine. In an average week this habitual caffeine drinker drinks at least one serving of a caffeinated beverage such as coffee, tea, or soda pop.

Electrophysiology testing. Electrophysiology (EP) testing is a valuable tool used for diagnosis of cardiac arrhythmias and evaluation of antiarrhythmic drug therapy (Levy, 1984). This technique studies the electrical activity of the heart by stimulating the myocardium with a temporary ventricular pacing wire in an attempt to induce arrhythmias. Programmed ventricular stimulation (introduction of rapid ventricular pacing and premature ventricular extra stimuli) is used to stimulate the ventricles and potentially produce arrhythmias (Vandepol et al., 1980). This method is used in this study to evaluate the arrhythmogenic effects of caffeine in individuals who have a history of documented ventricular arrhythmias.

Arrhythmias stimulated by electrophysiology testing. Non-sustained ventricular tachycardia is defined as ventricular tachycardia, at any rate, that terminates spontaneously. Sustained ventricular tachycardia is ventricular tachycardia, at any rate, that requires pharmacologic or electrical therapy for termination.

PVB and non-sustained ventricular tachycardia after caffeine administration have been reported in previous studies (Prineas et al., 1980; Dobmeyer et al., 1983; Sutherland et al., 1985). Premature atrial beats, atrial flutter-fibrillation, and paroxysmal supraventricular tachycardia have also been reported after caffeine administration (Josephson, & Stine, 1976; Dobmeyer et al., 1983; Myers, et al., 1987). These cardiac arrhythmias plus ventricular fibrillation can be induced by electrophysiologic testing.

CHAPTER II

Methods

Design

A quasi-experimental design was implemented in this study to investigate the effects of coffee in individuals who have a prior history of ventricular arrhythmias. The subjects were not randomly assigned to the experimental conditions; each subject received the same instituted treatment. The subjects acted as their own controls by participating in electrophysiology testing before and after caffeine ingestion. Caffeine, 275 mg, was given in the form of coffee (500 ml) to each subject after a caffeine-free electrophysiology test (control) and prior to a follow up electrophysiology test(caffeine test).

Subjects and Setting

The target population for this study was individuals who have a prior history of ventricular arrhythmias and who are habitual coffee drinkers. The pathology of their previous arrhythmias was cardiac in origin. The accessible population was individuals, with the above criteria, who were referred to the Oregon Health Sciences University (OHSU) for evaluation and treatment of their ventricular arrhythmias. These subjects were originally seen as in-patients on a medicine ward or in the CCU setting. The OHSU hospital is a 500-bed teaching hospital in Portland Oregon.

Twenty-five subjects were selected by convenience (nonprobability) sampling. Each subject was individually selected based on clinical judgment of his/her disease and physical status. The inclusion criteria consisted of the following rules:

1. Age between 35 and 80 years.
2. Habitual consumption of caffeine prior to origination of ventricular arrhythmia.
3. Cardiac origin of ventricular arrhythmias.
4. Heart rate and blood pressure stability as ascertained by the attending physician.
5. Normal plasma or serum electrolyte values (according to the OHSU clinical laboratory standards).
6. Electrophysiological test results during the caffeine-free test were one of the following: no arrhythmias, atrial arrhythmias, repetitive ventricular response, nonsustained ventricular tachycardia (terminates spontaneously), sustained ventricular tachycardia with easy conversion to the subject's baseline rhythm with burst pacing.

Individuals were excluded from the study based on the following criteria:

1. Pregnancy or lactation.
2. Documented psychological disorder.
3. Renal or hepatic failure.
4. Use of oral contraceptives, Cimetidine, Theophylline related drugs, Quinolone antibiotics.
5. Sustained ventricular tachycardia or ventricular fibrillation requiring cardioversion (to end the arrhythmia) during the initial or caffeine-free electrophysiology test.

Data Collection Procedures

The subjects were recruited from those already admitted to the OHSU hospital for elective electrophysiology testing. After an initial baseline electrophysiologic tests (first test of the electrophysiology protocol), patients

were selected for participation in the caffeine study using the inclusion/exclusion criteria check-list (see Appendix B). Informed consent procedures were followed with all participants in this study.

Two electrophysiology tests (caffeine-free test, and caffeine test) were part of this caffeine research study. For all patients undergoing electrophysiologic testing at OHSU, it is routine for them to have two baseline tests prior to antiarrhythmic drug testing. The second baseline electrophysiologic test was named the "caffeine-free test" for the purpose of this research study. In addition to the routine electrophysiology tests, the patients participated in one additional electrophysiology test (specifically for this research study) called the "caffeine-test". Other additions due to this study were cessation of caffeine intake 24 hours before the caffeine-free test and collection of blood samples prior to the caffeine-free and caffeine tests (which are described below).

Individuals who were admitted to OHSU were routinely prepared for electrophysiology testing by terminating all tobacco products and all antiarrhythmic drugs (excluding digoxin and calcium channel blockers) 36 hours prior to their initial test. Tobacco use was terminated because cigarette smoking is not allowed in the OHSU hospital setting. All individuals were routinely monitored with a bedside EKG oscilloscope or telemetry monitor during the antiarrhythmic drug free period. Patients who participated in the caffeine study were additionally required to stop the use of all caffeine-containing products at least 24 hours prior to the caffeine-free test. Caffeine withdrawal symptoms such as headache, irritability and drowsiness had the potential to occur among the subjects (Greden, 1979). Recording of caffeine withdrawal symptoms was not part of the protocol. Subjects who met the pre-established criteria received a detailed explanation of the caffeine research

study and then asked to participate. A consent form previously approved by the Human Research Committee of OHSU (see Appendix C) was signed by the participating individual.

The actual research study commenced within 24 hours of the patient's agreement to participate. The subjects had no oral intake for a minimum of 4 hours prior to each test. A supine position with the head of the bed elevated from 15-45 degrees was maintained for each subject 30 minutes before and during the caffeine-free test, during and after the coffee drinking period, and during the caffeine test. All patients had a previously placed hexapolar pacing wire in the right subclavian position. For routine electrophysiology testing, it was required for all patients to have intravenous (IV) access via an introducer side port, intrasil (long-arm catheter placed in central venous position), or a peripheral IV. The hexapolar pacing wire and intravenous line (central or peripheral) were routinely inserted in all patients undergoing electrophysiology testing and were not unique to this research study. This intravenous site was used for obtaining all blood samples (catecholamine, potassium, caffeine levels) during this study. Catecholamine levels were drawn from this indwelling catheter to avoid elevations in plasma values secondary to venipuncture. Venipuncture was performed in six subjects (27%) when blood samples could not be obtained from an indwelling line.

Immediately prior to the caffeine-free test 5 ml of blood were drawn and discarded from the indwelling catheter to ensure specimen integrity. Two and one half milliliters were then drawn and processed for later analysis of baseline plasma catecholamine and potassium levels. The caffeine-free test followed the standard electrophysiology test protocol. If during this baseline test the

subject developed ventricular tachycardia or fibrillation that required direct current cardioversion, the subject was excluded from the caffeine study.

Within 30 minutes after the caffeine-free test was completed, the fasting subject drank 500 ml of coffee (275 mg of caffeine) in less than 15 minutes. This serving of coffee was prepared by a recipe developed by the investigator (see Appendix D). The recipe was verified by laboratory measurements of the caffeine contents. The caffeine electrophysiology test took place 45 minutes after the caffeine was ingested or 60 minutes after coffee ingestion started. Directly before the caffeine electrophysiology test, 12.5 ml of blood were obtained from the indwelling catheter for plasma catecholamine, potassium and caffeine levels for later analysis (the initial 5 ml of this sample were discarded to ensure sample integrity). The caffeine test was conducted using the same protocol used for the baseline caffeine-free test.

The medical chart was reviewed for demographic data, medical history, and current medications by the researcher before the caffeine-free and caffeine tests (see Appendix E for chart review form). Within two days after the caffeine electrophysiology test was completed, the subject participated in a 5-10 minute interview with the researcher (see Appendix F). Questions related to caffeine ingestion, smoking history, and sleep/wake patterns were answered by the subject.

Coffee Preparation

Each subject was given a serving of coffee prepared by a standard recipe. This standard recipe was developed by contacting coffee companies (Yuban, Folgers, MJB) and requesting the amount of caffeine milligrams in a serving of coffee prepared by automatic drip (one tablespoon of ground coffee per 6 ounce serving). Yuban coffee (combination of arabica and robusta beans),

which has 81 mg of caffeine per serving, was selected. The researcher developed a recipe that produced a 500 ml serving of coffee that contained 275 mg of caffeine. To verify the milligrams per serving, three samples of coffee prepared by the calculated recipe were evaluated by high pressure liquid chromatography to determine the caffeine concentration. Standard servings of coffee were prepared in the CCU setting by the researcher. One teaspoon of sugar or 30 ml of milk were severed with the coffee upon request by the subject.

Instruments

Electrophysiology

The arrhythmogenic effects of caffeine were measured by electrophysiology testing using the following protocol. This testing procedure or programmed electrical stimulation measures the the severity and inducibility of ventricular arrhythmias.

Electrophysiology protocol. Electrophysiology testing involved right ventricular pacing using a standard protocol established at the Oregon Health Sciences University. Each test was completed in the CCU setting and lasted less than 30 minutes in duration.

Programmed ventricular stimulation. Extrastimuli were placed after six paced ventricular beats at two fixed cycle lengths (600 or 500, and 400 ms). A single ventricular extrastimulus (E1) was applied after the previous paced beats, followed by repetitive testing with shorter cycle lengths (using 10 ms intervals) until the ventricle was found to be refractory (ie. 400, 390, 380, etc.). If a single stimulus failed to initiate ventricular arrhythmias, then another ventricular extrastimulus (E2) was positioned 30 ms beyond ventricular refractoriness. This procedure was repeated for third and fourth extrastimuli (E3 and E4) until an endpoint was reached. Endpoint is defined as achievement of

a sustained ventricular arrhythmia or completion of the protocol through E4. All subjects were studied with a stimulation current strength of 1-5 mA using a digital stimulator that delivered rectangular pulses of 2 ms duration.

Reliability and Validity. Kudenchuk et al. (1986) evaluated the reproducibility of induced ventricular arrhythmias during electrophysiologic testing in the absence of drug therapy. Two baseline electrophysiology tests were performed within 6-24 hours in 114 subjects who had a previous history of ventricular tachycardia (n=53) or ventricular fibrillation (n=61). The inducibility of ventricular tachyarrhythmias increased as the number of programmed extrastimuli increased from one (10% induction) to four (64% induction) ($p \leq 0.02$). Arrhythmias induced with rapid ventricular pacing occurred 7% of the time with this patient population. Stimulated arrhythmias were more frequently nonreproducible (defined as a change in rate or duration) as the number of extrastimuli increased from one (7%) to four (27%). Nonreproducibility did not vary significantly between two, three and four extrastimuli. Arrhythmias with rapid ventricular pacing were nonreproducible 3% of the time. In conclusion, the reproducibility of electrophysiology testing is 73 to 97 percent. Reproducibility can be influenced by the stimulation protocol and the patient population. The protocol used by Kudenchuk et al. (1986) was implemented in this current caffeine study.

These inducibility and reproducibility electrophysiologic results are consistent with McPherson, Rosenfeld, and Batsford (1985) results. They studied the day-to-day reproducibility of right ventricular programmed stimulation in 77 patients. Fifty-three (80%) of 66 patients who had ventricular tachycardia during the first baseline electrophysiology test had ventricular tachycardia during the second baseline test (within 72 hours after the first test).

Reproducibility of these results were most probable if the ventricular tachycardia was induced with 1 or 2 programmed extrastimuli (95%). Only 14 of 25 patients (56%) who required 3 or more extrastimuli had reproducible results during the second baseline test.

The validity of this measurement has been confirmed by Vanderpol et al. (1980) who evaluated programmed ventricular stimulation with 529 patients. Ninety-one percent of patients who had clinical sustained ventricular tachycardia (SVT) (n=57) had inducible SVT with electrophysiology testing (n=52). In 12 of these instances, where the arrhythmia morphology was analyzed, the configuration of the inducible SVT was similar to that of the spontaneous clinical arrhythmia. Non-sustained ventricular tachycardia (NSVT) was induced in 62% of patients (n=18) who had symptomatic NSVT clinically (n=29). NSVT was induced in 0.7% of patients (n=3) who had no history of spontaneous ventricular tachycardia (n=443). Ninety-one percent of the clinically SVT patient group had organic heart disease; 47 patients (83%) had coronary heart disease and 38 (67%) had a left ventricular aneurysm.

Flame Emission Photometry

Plasma potassium was measured by flame photometry. The reference range for plasma potassium in adults is 3.5 to 4.5 mEq/L (mmol/L) (Tietz, Pruden, & Siggaard-Andersen, 1987). This laboratory measurement was performed on plasma obtained prior to the caffeine-free (baseline) and caffeine electrophysiology tests.

Specimen collection procedure for plasma potassium. A venous blood sample of 0.5 ml was drawn from an indwelling catheter and placed into a green stopper test tube that contained sodium heparin. The specimen was transported to the lab in less than 15 minutes. The sample was centrifuged

(room temperature) at 10,000 rpm for 5 minutes to separate the plasma from the formed elements. The plasma sample was frozen at -80 degrees Celsius until later assayed in a batched group. The plasma specimen was analyzed by spraying fine droplets of the sample from an atomizer into the propane-air flame of an automated flame photometer (Fisher Scientific, Tustin, CA).

Reliability and Validity. Reproducible and accurate flame photometry measurements are dependent on: careful cleaning of the instrument, proper adjustment of flame size and aspiration rate of the atomizer, warm-up period, thorough centrifugation of the plasma sample, and standardization (Tietz et al., 1987).

Ladenson, Apple, and Koch (1981) evaluated flame photometry and direct potentiometry measurements of serum potassium in subjects who had hyperlipemia. The potassium levels were found to be lower by 4-8 mmol/L after flame photometry than after direct potentiometry. Once the lipid was removed from the specimen of these hyperlipemia subjects, the potassium values were equal within 1-2 mmol/L. This artifactually low potassium value is due to a decrease in the percentage of water in the serum or plasma of the hyperlipemia specimens.

The validity of this flame photometry measurement of potassium has been confirmed by Langhoff and Steiness (1982) by comparing flame photometry with a potentiometric analyzer (Nova 1) in measurements of plasma, cerebrospinal fluid, and urine potassium. The flame photometry and Nova 1 measurement of plasma potassium, urine, or cerebrospinal fluid did not differ between the two study methods. These researchers also analyzed the influence of serum proteins and lipids on flame photometric and Nova 1 plasma potassium measurements. Human albumin or Intralipids were added to plasma

from a normal person (absence of paraproteinemia or hyperlipidemia) or to an aqueous potassium standards. The flame photometer analysis of potassium decreased linearly with increasing albumin content. At 50 gm of albumin per liter, the mean potassium measurement was 5.5% less with flame photometry and 1.0% less with Nova 1. An equivolume sample of plasma/intralipid reduced the potassium results by 16%. The Nova 1 results were not affected. These altered evaluation by flame photometer are a result of the relative decrease in sample water. Clinical difference between results by the two methods appear only in rare situations, such as hyperlipidemia and paraproteinemia.

High Performance Liquid Chromatography

Chromatography is a method that is used to separate and quantitate a wide variety of compounds, including hormones and therapeutic drugs. Catecholamine and caffeine levels were evaluated by this method in this research study. This method is popular because of its high sensitivity, high resolution, and short analysis time. High performance liquid chromatography (HPLC) separates mixtures of compounds by flowing liquid over a stationary phase. The quantity and quality of substance analysis depends on the chromatography techniques (Burtis, Bowers, Chattoraj, & Ullman, 1987).

When circadian timing is ignored, average values for norepinephrine and epinephrine concentrations are 150-300 pg/ml (0.89-1.77 nmol/L) and 20-60 pg/ml (109-327.5 pmol/L), respectively (Hjemdahl, 1984). Caffeine is not normally detectable in human plasma that has not been exposed to caffeine. Plasma caffeine will be measured in units of milligrams per liter (or micrograms per milliliter).

Specimen collection procedure. A venous blood sample of 2 ml was drawn for catecholamine levels from an indwelling catheter and placed into an

iced green stopper glass tube that contained sodium heparin. The tube was immediately transported to the laboratory (within 15 minutes) in an ice bath. The sample was placed in a refrigerated centrifuge for 10-15 minutes at 10,000 rpm and the plasma was separated from the cells. The plasma was frozen at -80 degree Celsius until the time of assay. Significant losses of catecholamine content can occur within 15-30 minutes after the specimen is collected if the plasma is not frozen immediately. Catecholamine samples also decay when the plasma is not separated from the cells immediately. When plasma specimens were frozen at -20 degrees Celsius for 11-106 days, the catecholamine content fell between 23-71% (Carruthers et al., 1970). Plasma catecholamine levels are stable for an indefinite time at -80 degrees Celsius. The HPLC instrument with reversed-phase separation and electrochemical detection (Bioanalytical Systems 400) was used for catecholamine analysis.

Reliability and validity of catecholamine measurements. According to the Operators Manual for this instrument, the retest reliability of this test is greater than 90%. Method reliability for catecholamine calculations is difficult to estimate because plasma catecholamine levels fluctuate rapidly and specimen handling can greatly influence the results of a measurement. One should also be cautious when validating the HPLC reversed-phase method because the retention patterns can be influenced by varying the pH of the mobile phase (which effects the ionization of the catecholamines) (Hjemdahl, 1984).

Goldstein, Feurerstein, Izzo, Kopin and Keiser, (1981) studied the HPLC technique against that of the catechol-O-methyl-transferase radioenzymatic (COMT-RE) assay. Plasma samples were taken from healthy, resting humans. The correlation between the two methods for both norepinephrine and epinephrine was 0.99. Reliability of catecholamine analysis were similar for

both methods, but the COMT-RE had lower coefficients of variation with measurements less than 100 pg/ml than the HPLC method. Both methods are accurate when measurements are greater than 100 pg/ml, and the COMT-RE is more accurate when values are less than 100 pg/ml. The advantages of the HPLC method are its speed, ease of sample preparation, low cost per assay, ease in trouble-shooting and the lack of radionuclide use. The procedure used for the HPLC in this study by Goldstein et al. (1981) is nearly exact to the procedures that were used in this present research study.

The specificity of the HPLC assay depends on the sample cleanup and concentration procedures, the chromatographic separation on the analytical column, and the selectivity afforded by the detector (Hjemdahl, 1984).

Specimen collection procedure for plasma caffeine. A venous blood sample of 3 ml was obtained from the indwelling catheter and placed in a grey stopper tube that contained potassium oxalate and sodium fluoride. The specimen was centrifuged (ambient temperature) at 25,000 for 5 minutes. The separated plasma was frozen at -80 degrees Celsius until analyzed in a batch at a later date. Long term stability of theophylline (chemically similar to caffeine) levels measured from frozen plasma has been established to be indefinite (measured in the OHSU clinical laboratory). The analysis of caffeine was similar to the procedure used for catecholamine calculations except detection was done with ultraviolet.

Reliability and validity of caffeine measurements. At the OHSU clinical laboratory, eleven monthly measurements of different sample with a known concentration of caffeine were analyzed. The laboratory values had a mean difference of 0.46 ± .18 mg/L (SEM) when compared to the target values.

Foenander, Birkett, Miners, and Wing (1980) did micro-scale determinations of xanthines with reversed phase HPLC. They were able to detect quantitations as small as 0.1 mg/L for caffeine, theophylline, and theobromine. This method also correlated well (r=0.98) with an enzyme multiplied immunoassay technique, when 40 samples of a xanthine member, theophylline, were measured. The reproducibility of this method for measuring caffeine was determined by analyses of replicates at concentrations of 1.0 and 20 mg/L. Intra-assay coefficients of variations for caffeine were 3.8% at 1 mg/L and 2.7% at 20 mg/L.

Blanchard, Mohammadi, and Conrad (1980) evaluated three specimens with reversed-phase HPLC. A specimen consisted of a standard mixture of xanthines, or a drug free plasma sample, or a drug free plasma supplemented with the standard mixture of xanthines. The specimens were analyzed and caffeine concentrations were determined. The possible metabolites of caffeine and other plasma constitutes did not interfere with the analysis of caffeine. This method of analysis (HPLC) was able to accurately separate and measure caffeine.

Chart Review

A medical chart review instrument was used to obtain the subject's age, sex, body mas, medical history and current medications (Appendix E). The information was collected by the researcher before the caffeine-free electrophysiology test. This information was used to describe the sample population. This tool was reviewed by three clinical experts (nurses with cardiology experience) to determine its content validity prior to its use in the study.

Interview Questionnaire

A caffeine intake questionnaire was used during a 5 to 10 minute interview. This questionnaire measured the subjects' daily coffee intake prior to and after their initial event of ventricular arrhythmias. It also measured caffeine intake of other caffeine containing beverages, chocolate food items, and medications. The interview was conducted by the researcher after the caffeine electrophysiology test. Cigarette smoking status and sleep/wake patterns were assessed during this time. This interview questionnaire was reviewed by three clinical experts to determine its content validity prior to its use.

Analysis of Data

The information gained from the interview questionnaire and the chart review was analyzed by descriptive statistics. The subjects were described by tabulation of nominal and ordinal data and calculation of mean and range values. The subjects' caffeine intake was categorized according to the following classifications: (a) 0-100 mg caffeine intake per day, (b) 101-400 mg of caffeine intake per day, (c) greater than 400 mg caffeine intake per day. The amount of caffeine in milligrams that was assigned to various beverages, food items and medications is presented in Appendix G.

For the purpose of this study, the electrophysiology, caffeine, catecholamine, and potassium results were documented on a result sheet (see Appendix H). These results were analyzed according to the hypotheses.

Scoring method for electrophysiologic testing. The severity of the induced arrhythmia was classified according to the arrhythmia scoring system (see Appendix A) devised by Kudenchuk et al. (1986). The type of rhythm was classified on a 1 to 8 scale, with 8 being the most severe rhythm. The inducibility scoring system was developed by this researcher (see Appendix A). The

number of extrastimuli used to induce the rhythm was classified on a 1 through 4 scale, with 4 representing an arrhythmia that was easy to induce. A score of 2 represents a decrease in inducibility ease.

Revision of Severity Scoring Method

According to Kudenchuk et al. (1986), a change in severity score of less than three units in either direction was not felt to be reproducible on repetitive testing, and therefore not significant. This suggests that the scoring system could be modified with compression of the scores into fewer categories (noninduced, nonsustained VT, sustained VT). A revised scoring method (see Appendix I), along with Kudenchuk's scoring method were used to evaluate the data. This revised scoring method was developed so that rhythms with similar clinical meaning could be grouped together.

The three classifications of ventricular arrhythmias are: 1) noninduced: none, single to triple repetitive PVB, 2) nonsustained VT: four to less than 30 seconds of ventricular tachycardia, 3) sustained VT: greater than or equal to 30 seconds of ventricular tachycardia or ventricular fibrillation. These classifications are based on clinical symptoms and/or hemodynamic stability. The definition of these ventricular arrhythmias are similar to those used by Wellens, Brugada and Stevenson (1985). Instead, they define nonsustained VT as greater than five repetitive beats to less than 30 seconds duration of VT.

By revising the Kudenchuk scoring method to support these clinical observations or groupings (see Appendix A and I), scores 1 and 2 were combined, scores 3 and 4 were combined and scores 5 and 6 were combined. Hemodynamic instability during sustained VT is dependent on the rate of the tachycardia, the presence and degree of underlying heart disease, peripheral vascular disease as well as the duration of the tachycardia and mode of spread

of the depolarization wave across the myocardium (Raichlen, Links & Reid; 1985). Therefore, the separation of VT rates into three scores was maintained for the revised scoring system. This revised scoring system allows non significant arrhythmia changes to be discarded.

The highest severity and inducibility scores that were achieved at the completion of programmed ventricular stimulation were defined as the cumulative rhythm score for that particular test. The caffeine-free test scores were compared to the caffeine test scores in relation to the severity and inducibility. The final score was either a positive or negative score that reflected the change in severity and inducibility of ventricular arrhythmias after coffee.

Hypotheses 1 & 2. In evaluating the severity and inducibility of arrhythmias before and after caffeine ingestion each subject was assigned a set of scores as described in the scoring methods (above). Frequency distributions of changes in severity and inducibility scores after caffeine were constructed. To determine the significance of the caffeine induced arrhythmias in relation to severity and inducibility, Wilcoxon summed-rank test was used. A p value of 0.05 or less was considered significant.

Hypotheses 3 & 4. The subjects' catecholamine level were measured immediately prior to the ingestion of coffee and one hour after coffee. The induced arrhythmias after caffeine were classified according to the severity and inducibility scores (as previously described). Catecholamine effects on arrhythmias were analyzed by comparing changes in severity and inducibility scores to increased changes in epinephrine and norepinephrine plasma levels. Spearman-rank order correlation analysis was used to determine the significance of this relationship. A p value of 0.05 or less was considered significant.

Hypotheses 5 & 6. The effect of coffee on potassium and arrhythmias were analyzed in a manner identical to that used for catecholamines. Potassium effect on induced arrhythmias was analyzed by comparing changes in severity and inducibility score to decreased changes in potassium plasma levels. Again, Spearman-rank order correlation analysis was used to determine the significance of this relationship. As before, a p value of 0.05 or less was considered significant. In addition, the relationship between catecholamine changes and potassium changes was described graphically.

If atrial arrhythmias occurred, they were classified as an non-induced arrhythmia and were evaluated separately from ventricular arrhythmias. No atrial arrhythmias occurred during the caffeine-free or caffeine electrophysiology tests.

T-test analysis was used to assess the differences in mean catecholamine and potassium values. Theses values were measured before and after caffeine. The rationale for using the above statistics is discussed in the results section.

Protection of Human Subjects

The privacy of each subject was maintained by assigning an identification number. Information concerning the subject was kept strictly confidential. The subject's name, hospital unit number, social security number, or other personal identification will not be presented to the public or published in a journal.

The subject signed an informed consent form that stated the purpose of the research study, the procedures involved, and risk and benefits of the study. Each subject received a detailed explanation of the study, and was given the opportunity to consult with other health care practitioners as needed. The subject could withdraw from the study at any time.

The risks associated with electrophysiologic procedures have been reported by Dimarco, Garan, and Ruskin (1982) who performed 1062 intracardiac electrophysiologic procedures in 359 patients. In ten percent of the procedures performed, sustained ventricular arrhythmias were induced and direct-current countershock was required to correct the arrhythmia. This represented 17% of the patient population. No patient needed cardiopulmonary resuscitation, and there were no complications of myocardial/cerebral infarction or cerebral/systemic arterial embolus. In 20 patients (5.6%), complications related to electrophysiologic procedures were identified: deep venous thrombosis, pulmonary emboli, catheter (pacing wire) site infection, systemic infection, and pneumothorax. Thromboembolic event (2.5%) was the most common complication followed by pneumothorax (1.6%). Despite the possibility of life-threatening arrhythmias, no mortality was associated with the induction of arrhythmias in the cardiac laboratory.

Each subject in this research study was informed about life threatening arrhythmias and how he/she would be protected from unfavorable consequences. Programmed ventricular stimulation was performed by a trained cardiologist with the presence of a critical care nurse. All electrophysiology testing done with standard monitoring and resuscitation equipment. The bedside was equipped with an oxygen source, ambu bag, and suction equipment. Direct-current countershock equipment was immediately available and ready to use if necessary. Rapid ventricular pacing (burst pacing) was used first to convert the ventricular tachycardia rhythm. Five subjects who had sustained ventricular tachycardia during electrophysiology testing were converted to sinus rhythm by burst pacing. Direct current countershock was available if burst pacing was not successful. Midazolam 5-10 mg, a short acting

benzodiazepine, was available to use for sedation prior to countershock. If ventricular tachycardia with hemodynamic decompensation does not respond to 100, 200 or 400 joules of countershock, advanced cardiac life support (ACLS) would have been initiated. Intravenous propranolol would have been added to the ACLS protocol if previous interventions were not successful in terminating the arrhythmia. Beta-adrenergic blockade reverses all of the electrophysiologic effects of epinephrine (Morady et al., 1988) and converts caffeine induced VT to normal sinus rhythm (Weesner, Denison, & Roberts, 1982). Advanced cardiac life support was not necessary during electrophysiology testing.

Before participating in this research study, the subjects had already been informed of the risks related to long term indwelling catheter and pacing wire placement. The complications (catheter skin infection, systemic infection, and thromboembolic events) documented by Dimarco et al. (1982) and the follow-up treatments were previously discussed with each subject. The risks of arrhythmias and discomforts related to caffeine ingestion were outlined in the consent form and discussed with each subject.

The subject gained personal benefits from this study by acquiring knowledge about caffeine and its effect on ventricular arrhythmias in him/herself. The information gained from this study is helpful in the advancement of medical knowledge. Health care practitioners can determine if caffeine imposes an additional risk to the cardiac patient who has a history of ventricular arrhythmias. Practitioners can also determine if caffeine intake interferes with electrophysiologic testing interpretation.

This research study imposed some additional risk of electrical hazards to the patient. Electrical safety was implemented according to the OHSU policy.

All electrical devices were assessed for safety before use by the hospital Clinical Engineering Department. Electrical equipment that is used near the subject had an extra ground plug for the electrical outlet. All EKG monitoring equipment contained a ground electrode lead. Electrical shocks did not occur in any subjects during this study. Standard blood precautions were observed.

Threats to Internal and External Validity

The internal validity threat that might have influenced the experimental outcome of this study was the selection of subjects. Patients were selected to participate in the study if they meet the established inclusion and exclusion criteria. The results of this study represent individuals who have a history of arrhythmias and are medically stable. Subjects who were excluded from the study were patients who were at high risk for sustained arrhythmias. Because these individuals are excluded, the effects of caffeine on arrhythmias do not reflect the total population of ventricular arrhythmias patients.

The external validity threats to the study that might have influenced the generalizability of the study results are the Hawthorne effect and the interaction of history and treatment. The subjects participating in this study knew they were involved in a study and this may have caused their plasma catecholamine levels to increase above normal and possibly increase the likelihood for arrhythmias. The ingestion of coffee during hospitalization is different from ingestion of coffee in a natural environment, such as home. This may have interfered with test and application of results.

Controlling for Error and Bias

A quasi-experimental design was chosen for this research study. This type of design is less desired because it lacks randomization of the treatment condition. The subjects were selected by convenience sampling. This

selection method is weaker than probability sampling. The study design and selection method were specifically chosen because of ethical concerns. The target population was patients who were at risk for arrhythmias because of their medical history; careful selection was necessary so that extremely high risk individuals will not be exposed to the stimulating beverage, coffee. Each patient acted as his/her own control, therefore randomization of the treatment was not implemented. This avoids the ethical issue of exposing some patients to a higher risk than other patients.

An interview with the subject was performed to collect individual caffeine consumption histories. This type of data collection method may have encouraged biased response by the subject. The interaction between the interviewer and the subject may have affected the subject's response. Furthermore, the accuracy of information provided by the subjects may have been negatively influenced by poor memory recall.

CHAPTER III

Results

Description of the Sample

Characteristics of Sample

The study population was composed of 22 adults who were hospitalized for elective evaluation of ventricular arrhythmias with electrophysiological testing. The participants ranged from 39 to 72 years of age (see Table 3). The mean age was 60.4 ±10.3 years. The most common age group was 65 to 74 year olds (46%). The sample population consisted of 91% males (n=20) and 9% females (n=2). Thirty-three percent of the total group smoked cigarettes prior to hospitalization. All subjects, except one, were day schedule people with night hour sleeping patterns. During hospitalization, the single night schedule subject was forced to follow a day time schedule. His normal sleeping hours were 12 noon to 6 PM outside of the hospital. At the time of the caffeine test, this subject had been hospitalized for one night and two days.

The interview questionnaire demonstrated that 46% of the subjects consumed 101-400 mg of caffeine per day and 50% consumed greater than 400 mg of caffeine per day prior to having a problem with ventricular arrhythmias (see Table 3). After an event of ventricular arrhythmias, or prior to this current hospitalization, 50% of the total population consumed 0-100 mg of caffeine per day. Further data showed that 36% of the subjects consumed 101-400 mg of caffeine per day and 14% consumed greater than 400 mg per day prior to hospitalization.

Table 3

Characteristics of the Sample

Characteristics		n	%
Age	35-44	2	9
	45-54	3	14
	55-64	7	31
	65-74	10	46
Gender	male	20	91
	female	2	9
Current Cigarette Smoker	yes	7	33
	no	14	67
Sleep/Wake Patterns	night sleeper	21	96
	day sleeper	1	4
Daily Caffeine Use Prior to Arrhythmia Problem	0-100 mg	1	4
	101-400 mg	10	46
	> 400 mg	11	50
Daily Caffeine Use Prior to Hospitalization	0-100 mg	11	50
	101-400 mg	8	36
	>400 mg	3	14

Cardiac Characteristics of Sample

All subjects in this study had a history of heart disease (see Table 4). Nineteen (86%) participants had Coronary Artery Disease (CAD), two (9%) had mitral valve disease, and one (4%) had a history of palpitations and syncope. Other cardiac problems present among this population sample were history of myocardial infarction (64%), congestive heart failure (18%), hypertension (27%), and left ventricular aneurysm (18%). Ejection fractions were obtained for eight subjects and they ranged from 0.15 to 0.74 (mean ejection fration = 0.41). Almost all of the subjects had normal sinus rhythm as a baseline heart rhythm. Twenty-seven percent of the total group had a history of atrial fibrillation or atrial tachycardia. The clinical arrhythmia that initiated electrophysiological testing was ventricular tachycardia in 55% of the population, nonsustained ventricular tachycardia in 23% of the subjects and ventricular fibrillation in the remaining 23% of the group. A clinical rhythm is defined as an arrhythmia that occurs spontaneously. Nearly 64% of the subjects had syncope with their clinical arrhythmias. Ventricular arrhythmias were newly diagnosed in greater than 50% of the population.

During electrophysiological testing all antiarrhythmic medications were held during the caffeine-free and caffeine tests, including beta blockers. Some subjects were receiving other cardiac medications that were continued during the testing period. These medications were calcium channel blockers (36%), digoxin (23%), nitrates (9%), diuretics (23%), and ACE inhibitors (18%). Other medications taken during the testing period, that could effect the metabolism of caffeine, were zantac (14%), cimetidine (4%), premarin (9%), and xanax (4%). As discussed earlier, cimetidine,

Table 4
Cardiac History of the Sample

Characteristic		n	%
Heart Disease	CAD	19	86
	valvular	2	9
	syncope/palpitations	1	4
Other Cardiac Problems	CHF	4	18
	MI	14	64
	HTN	6	27
	aneurysm	4	18
Baseline Heart Rhythm	normal sinus	21	96
	atrial fibrillation	1	4
Atrial Arrhythmia History	yes	6	27
	no	16	73
Presenting Arrhthmia	NSVT	5	23
	VT	12	55
	VF	5	23
History of Syncope	yes	14	64
	no	8	36
Length of Arrhthymia Problem	< 2 weeks	12	55
	2-4 weeks	1	4
	5-52 weeks	6	27
	> 1 year	3	14
Current Cardiac Medications	calcium channel blocker	8	36
	digoxin	5	23
	nitrates	2	9
	diuretic	5	23
	ACE inhibitor	4	18
Other Medications	Zantac	3	14
	Cimetidine	1	4
	Premarin	2	9
	Xanax	1	4

pregnancy, and oral contraceptives will prolong the half-life of caffeine by inhibiting caffeine metabolism (Facts and Comparison, 1984). It is not known whether zantac or premarin may have the same effects on caffeine. Xanax depresses the central nervous system (USP DI, 1989). It is not known whether xanax will decrease the effects of caffeine on catecholamine concentrations.

Data

Caffeine Data

All subjects received a serving of coffee that was prepared with a standard coffee recipe (see Appendix D). To determine the caffeine content of a serving of coffee from the recipe, three different samples were measured by HPLC. These measurements were done prior to the initiation of the research study. See table 5 for caffeine values of the three samples. The mean content of caffeine per serving from the recipe samples was 550 ± 11.5 mg/L. During the study period, each subject received approximately 275 mg of caffeine per 500 ml serving of coffee.

Caffeine plasma levels, one hour after initiation of coffee drinking or 45 minutes after completion of coffee, ranged from 2.7 mg/L to 12.4 mg/L. The mean caffeine level was 6.2 ± 0.5 (SEM). A nonlinear relationship exist between individual body mass indexes (BMI) and plasma caffeine concentrations (Figure 3). BMI is a measurement of body mass that is derived from body weight and height. This index is commonly used above other measurements of body mass (skin fold thickness, water displacement, weight alone) because it is based upon muscularity and bone structure and is accurate and easy to use (Khosla & Lowe, 1967; Thomas, McKay & Cutlip, 1976).

The plasma caffeine levels were measured by HPLC in batched groups (n=10). Each sample was standardized with a quality control sample (5 mg/L).

Table 5

Caffeine Content of Prepared Coffee

Sample	Caffeine mg/L
1	541
2	563
3	546
mean	550 ±11.5
mean caffeine content per 500 ml	275

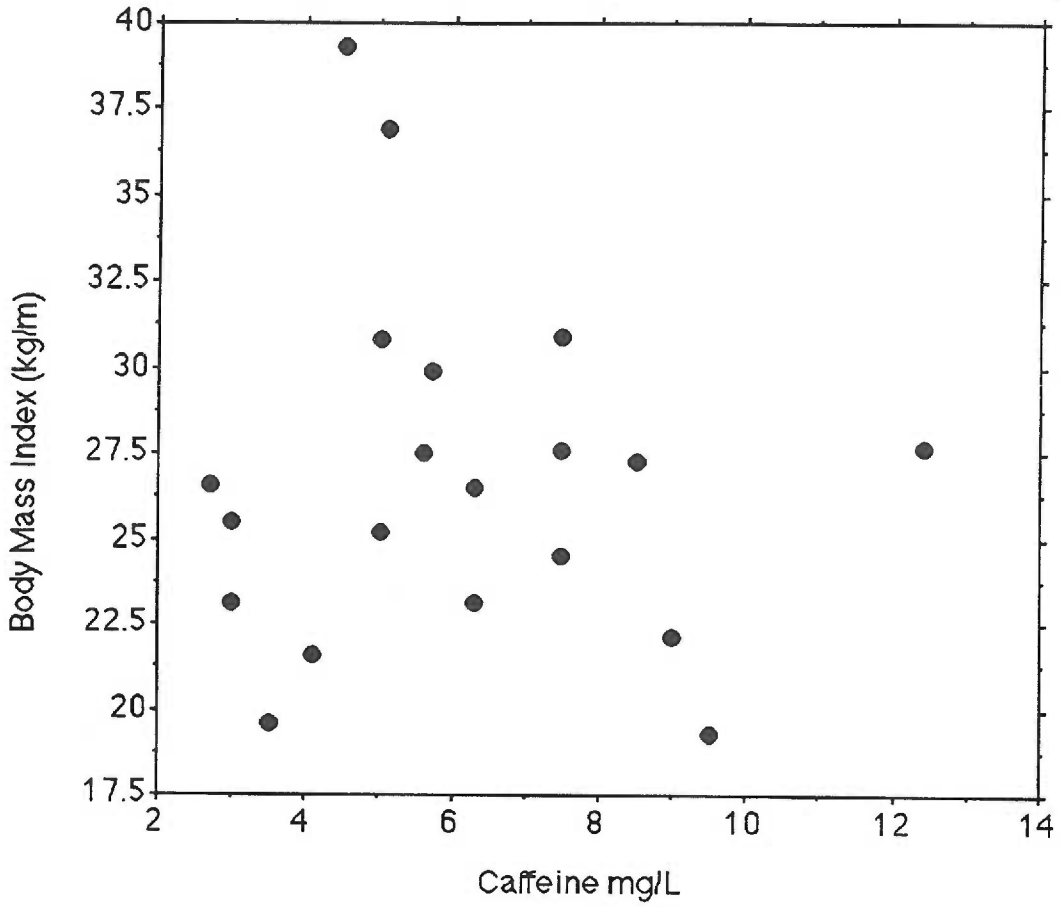

Figure 3. Relationship between body mass index (BMI) and plasma caffeine levels.

The assay mean value was 5.49 ± 0.43 (S.D.) mg/L. The coefficient of variation of the control was 8%. The intra-assay variability of five caffeine samples was 6.5%.

Electrophysiologic Data

Before and after caffeine ingestion, electrophysiology testing was performed with each subject. Table 6 shows the individual results of the caffeine-free and caffeine electrophysiology test using the Kudenchuk scoring method.

The changes in Kudenchuk severity scores are presented in Figure 4. Fourteen (64%) subjects showed no change in their electrophysiology severity scores when measured before and after caffeine ingestion. Six (27%) subjects had a negative change in severity score; their ventricular arrhythmias were less severe after drinking coffee. Only 2 (9%) subjects had a positive change in their severity scores after caffeine; ventricular arrhythmias became more severe after coffee. There was no statistically significant difference between the control group and the study group in relation to the severity of ventricular arrhythmias ($p>0.05$) with Wilcoxon summed rank analysis. Therefore, this does not support the hypothesis that cardiac patients with a history of ventricular arrhythmias have more severe arrhythmias after consuming coffee with 275 mg of caffeine.

The new revised severity scoring system (see Table 7 and Figure 5) decreased the number of negative changes in scores (less severe arrhythmias) from six (27%) to three (14%). The two (9%) positive changes in scores (more severe arrhythmias) remained unchanged. The remaining 77% of the subjects had unchanged severity scores after caffeine. By using the revised scoring method, there was no statistically significant difference between the control

Table 6
Electrophysiology Testing Before and After Caffeine

Subject	Caffeine-free Test			Caffeine Test			Score	
	Rhythm	Rate	Extrastimuli	Rhythm	Rate	Extrastimuli	Severity*	Inducibility
1	R1		E2	0		E4	-1	-2
2	R2		E2	N11		E2	2	0
3	N4		E2	R3		E2	-1	0
4	R2		E1	0		E4	-1	-3
5	SVT	250	E4	SVT	280	E3	0	1
6	N4		E4	R2		E3	-1	1
7	R2		E1	R2		E1	0	0
8	R2		E3	R2		E3	0	0
9	R1		E1	R2		E2	0	-1
10	SVT	230	E2	SVT	250	E2	0	0
11	R2		E1	R1		E2	0	-1
12	N9		E3	N4		E2	-1	1
13	SVT	220	E2	SVT	220	E2	0	0
14	SVT	200	E4	R2		E1	-4	3
15	R2		E1	R2		E1	0	0
16	N27 Sec.		E2	N25		E2	0	0
17	R1		E3	R1		E3	0	0
18	R1		E1	N4		E4	1	-3
19	N7		E4	N8		E3	0	1
20	R3		E3	R2		E3	0	0
21	SVT	210	E4	SVT	240	E2	0	2
22	R2		E1	R1		E2	0	-1

* Kudenchuk scoring method (refer to text)

E=extrastimuli, N=nonsustained VT, R=repetitive ventricular response, SVT=sustained VT

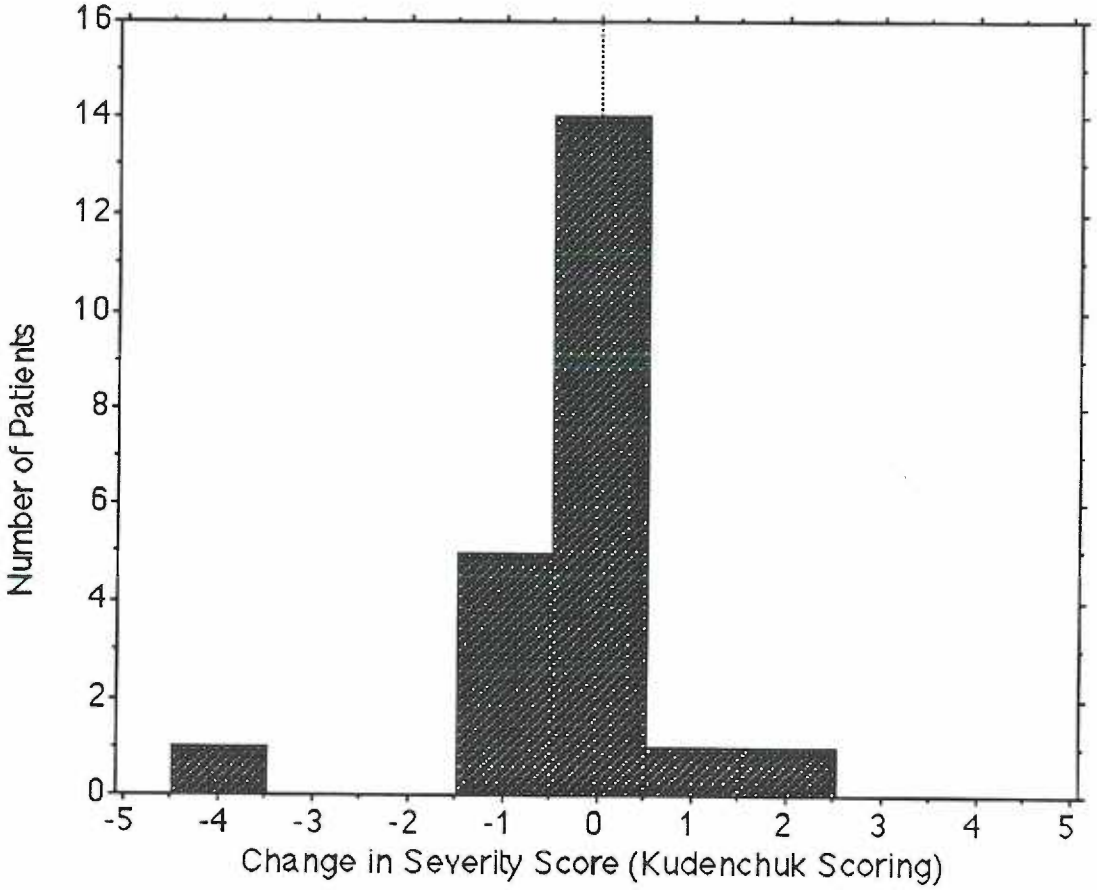

Figure 4. Frequency of changes in severity scores measured before and after caffeine.

Table 7
Electrophysiology Testing Before and After Caffeine

Subject	Caffeine-free Test			Caffeine Test			Score	
	Rhythm	Rate	Extrastimuli	Rhythm	Rate	Extrastimuli	Severity*	Inducibility
1	R1		E2	0		E4	0	-2
2	R2		E2	N11		E2	1	0
3	N4		E2	R3		E2	-1	0
4	R2		E1	0		E4	0	-3
5	SVT	250	E4	SVT	280	E3	0	1
6	N4		E4	R2		E3	-1	1
7	R2		E1	R2		E1	0	0
8	R2		E3	R2		E3	0	0
9	R1		E1	R2		E2	0	-1
10	SVT	230	E2	SVT	250	E2	0	0
11	R2		E1	R1		E2	0	-1
12	N9		E3	N4		E2	0	1
13	SVT	220	E2	SVT	220	E2	0	0
14	SVT	200	E4	R2		E1	-3	3
15	R2		E1	R2		E1	0	0
16	N27 Sec.		E2	N25		E2	0	0
17	R1		E3	R1		E3	0	0
18	R1		E1	N4		E4	1	-3
19	N7		E4	N8		E3	0	1
20	R3		E3	R2		E3	0	0
21	SVT	210	E4	SVT	240	E2	0	2
22	R2		E1	R1		E2	0	-1

* Revised scoring method (refer to text)

E=extrastimuli, N=nonsustained VT, R=repetitive ventricular response, SVT=sustained VT

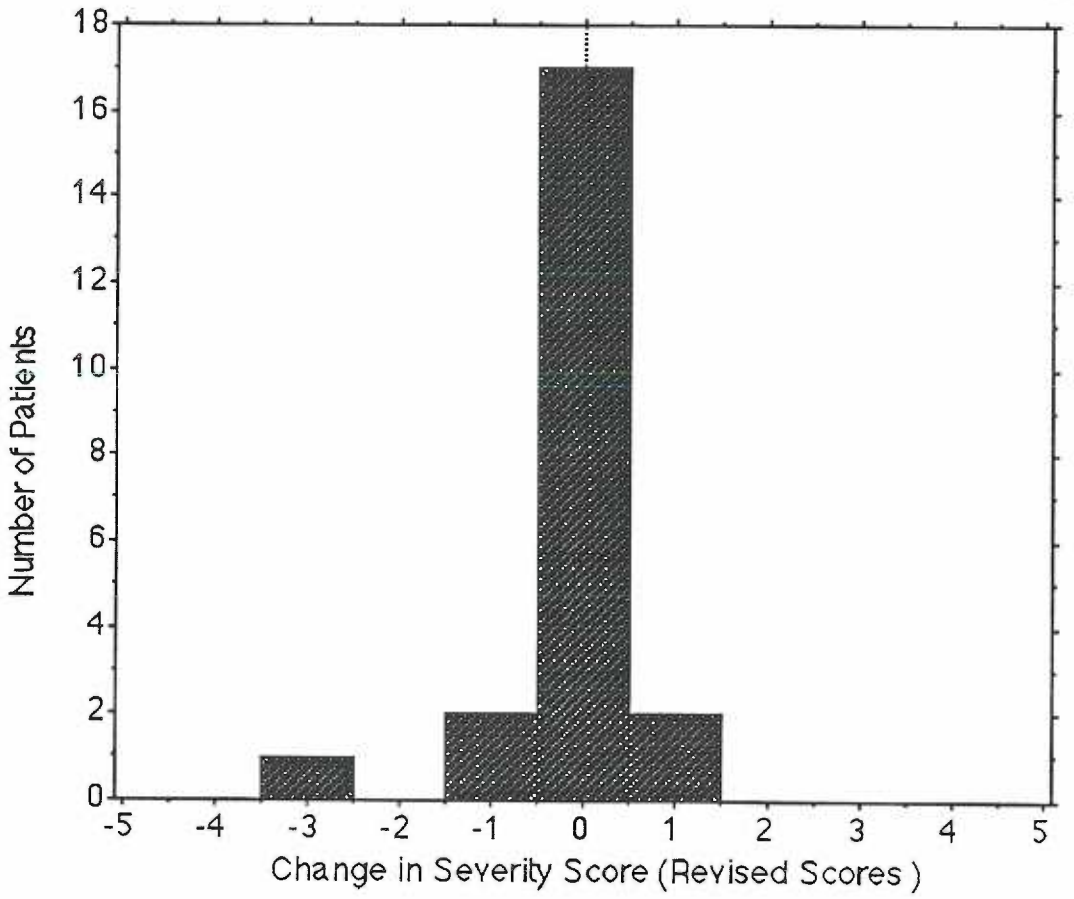

Figure 5. Frequency of changes in severity scores measured before and after caffeine

group and the study group in relation to the severity of ventricular arrhythmias ($p>0.05$) with Wilcoxon summed rank analysis.

The differences in inducibility scores when measured before and after caffeine are displayed in Figure 6. Ten (46%) subjects showed no change in inducibility of ventricular arrhythmias after caffeine. Six (27%) subjects had a negative change in their inducibility score after caffeine. These subjects had a decrease in ease of inducibility. Six (27%) subjects had a positive change in their scores. Induction of ventricular arrhythmias become easier after caffeine consumption in these subjects. As determined by Wilcoxon summed rank analysis, there was no statistically significant difference between the caffeine-free and caffeine group ($p>0.05$). This does not support the hypothesis that cardiac patients with a history of ventricular arrhythmias have more easily induced arrhythmias after 275 mg of caffeine in coffee form.

Catecholamine Data

Measurements of plasma epinephrine and norepinephrine values were obtained prior to caffeine and one hour after caffeine consumption. The coefficients of variation for epinephrine and norepinephrine assays were 7.1% and 4.1%, respectively. These variabilities were calculated from repeated assays from three human plasma samples.

The mean plasma epinephrine level before caffeine was 401.2 ± 108.5 (S.E.M.) pg/ml for 17 samples. The values ranged from 47.7 to 1915.6 pg/ml. The intra-assay variability was 14.2% for six samples . The mean plasma epinephrine level after caffeine was 394.6 ± 82.7 (S.E.M.) pg/ml. These values ranged from 101.3 to 1269.9 pg/ml. The intra-assay variability was 10.6% for six repeated

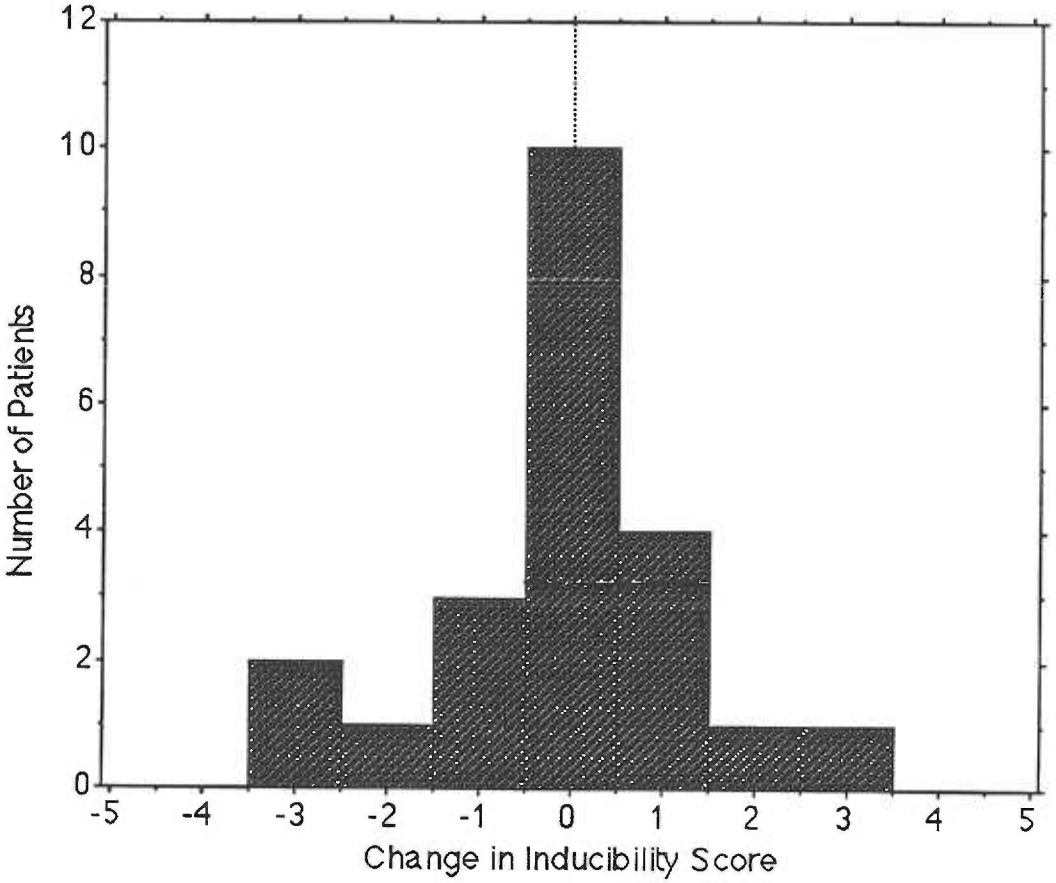

Figure 6. Frequency of changes in inducibility scores measured before and after caffeine.

samples. See Figure 7 for changes in mean epinephrine before and after caffeine. A directional paired t-test showed no statistical difference in the mean epinephrine values (p=0.46). The mean change in epinephrine values before and after caffeine was -6.6 ± 65 (S.E.M.) pg/ml.

The mean plasma norepinephrine level before caffeine was 559.2 ± 65.1 (S.E.M.) pg/ml for 17 samples. The values ranged from 242.5 to 1293.6 pg/ml and the intra-assay variability was 6.8% with six samples. After caffeine, the mean norepinephrine value increased to 625.3 ± 69.1 (S.E.M.) pg/ml. The values ranged from 247.3 to 1235.2 pg/ml with an intra-assay variability of 6.2% with six samples. Figure 8 shows the differences in means for norepinephrine values before and after caffeine. A directional t-test showed no statistical difference in the mean norepinephrine values (p=0.053). The mean change in norepinephrine values before and after caffeine was 66.1 ± 38.7 (S.E.M.) pg/ml.

The relationship between increased catecholamine values and ventricular arrhythmias (severity and inducibility) was assessed with Spearman's Rank order correlation. There was no statistical significant correlation between increased catecholamines and severity or inducibility of ventricular arrhythmias ($p>0.05$). The individual correlation values were as follows: epinephrine and severity $r_S = 0.24$; epinephrine and inducibility $r_S = -0.22$; norepinephrine and severity $r_S = 0.49$; norepinephrine and inducibility $r_S = 0.41$. The correlation values for severity were calculated from the revised scoring method and not the Kudenchuk scoring method. These data do not support the hypotheses that cardiac patients with a history of ventricular arrhythmias, who have increased plasma catecholamine (epinephrine or norepinephrine) values one hour after caffeine, have increased severity or increased ease in inducibility of ventricular arrhythmias.

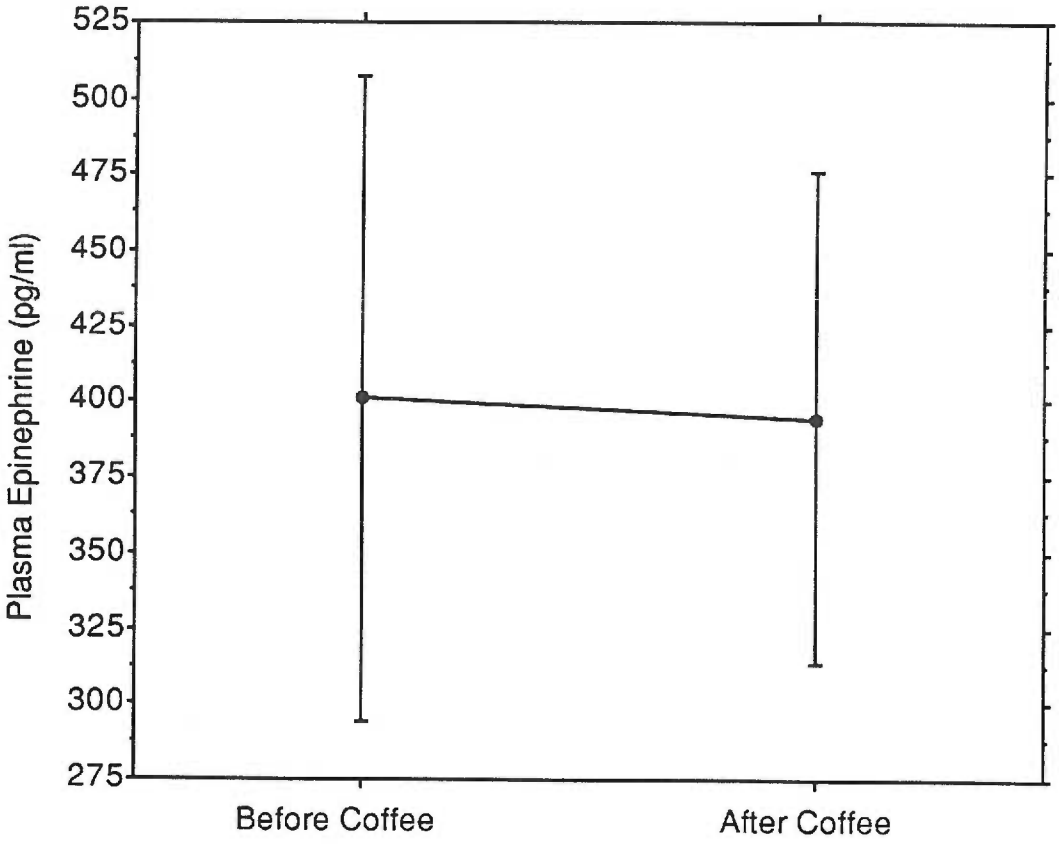

Figure 7. Mean plasma epinephrine (± S.E.M.) before and after coffee.

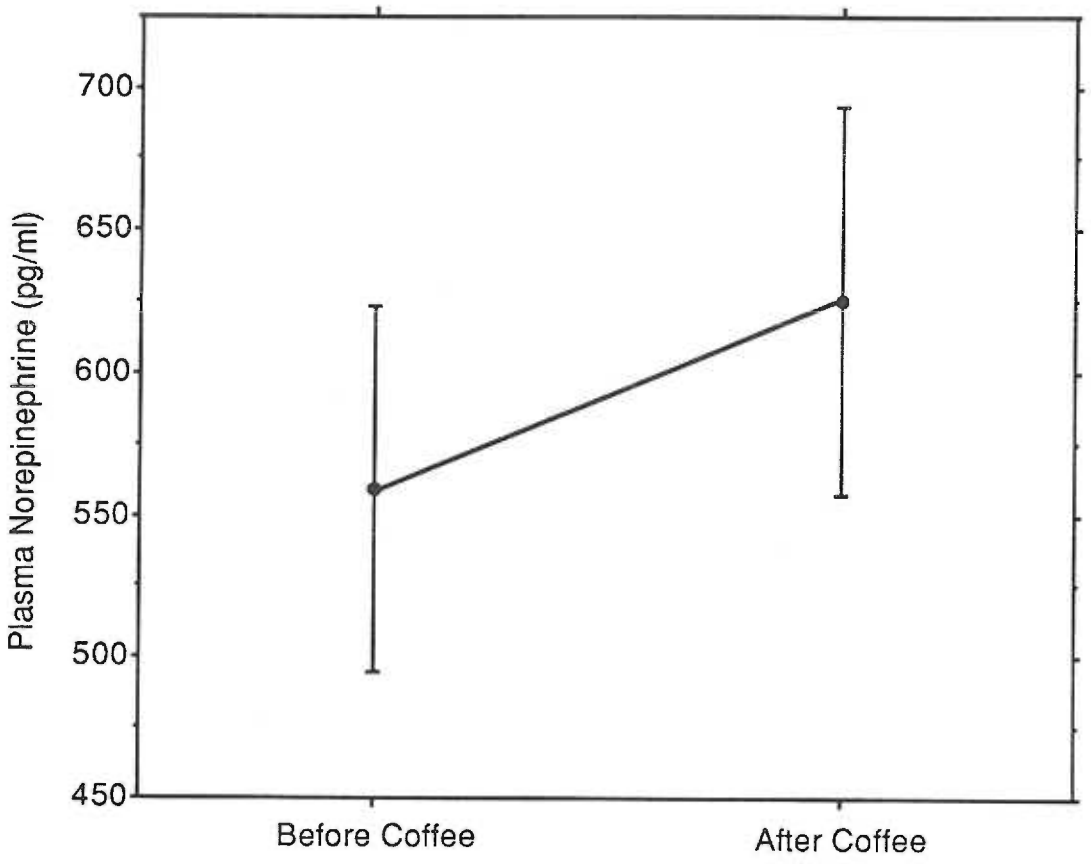

Figure 8. Mean plasma norepinephrine (±S.E.M.) before and after coffee.

Potassium Data

Plasma potassium levels were measured by flame emission photometry before caffeine and one hour after caffeine consumption. The coefficient of variation for this analysis was 3.1% .

The mean potassium level, prior to caffeine intake, was 4.06±0.1 (S.E.M.) meq/L with a range from 3.3 to 4.8 meq/L (18 samples). The intra-assay variability was 2.2% for 16 samples. After caffeine, the mean level was 4.10±0.1 (S.E.M) meq/L with a range of 3.7 to 4.5 meq/L (see Figure 9). The intra-assay variability was 2.5% for 15 samples. The mean change in potassium values before and after caffeine was 0.048±0.1 (S.E.M.) meq/L. There was no significant change in the mean plasma potassium value ($p=0.18$) by t-test analysis. Potassium concentrations decreased in six subjects and increased in 12 subjects after caffeine ingestion.

Spearman's Rank order correlation was used to determine if there was a relationship between decreased changes in potassium levels and ventricular arrhythmias (severity or inducibility). There was no statistically significant correlation between decreased potassium values and severity ($r_s=0.51$) or inducibility ($r_s=0.23$) of ventricular arrhythmias ($p>0.05$). This conclusion does not support the hypotheses that cardiac patients with a history of ventricular arrhythmias, who have decreased plasma potassium values one hour after caffeine, have increased severity or increased ease in inducibility of ventricular arrhythmias.

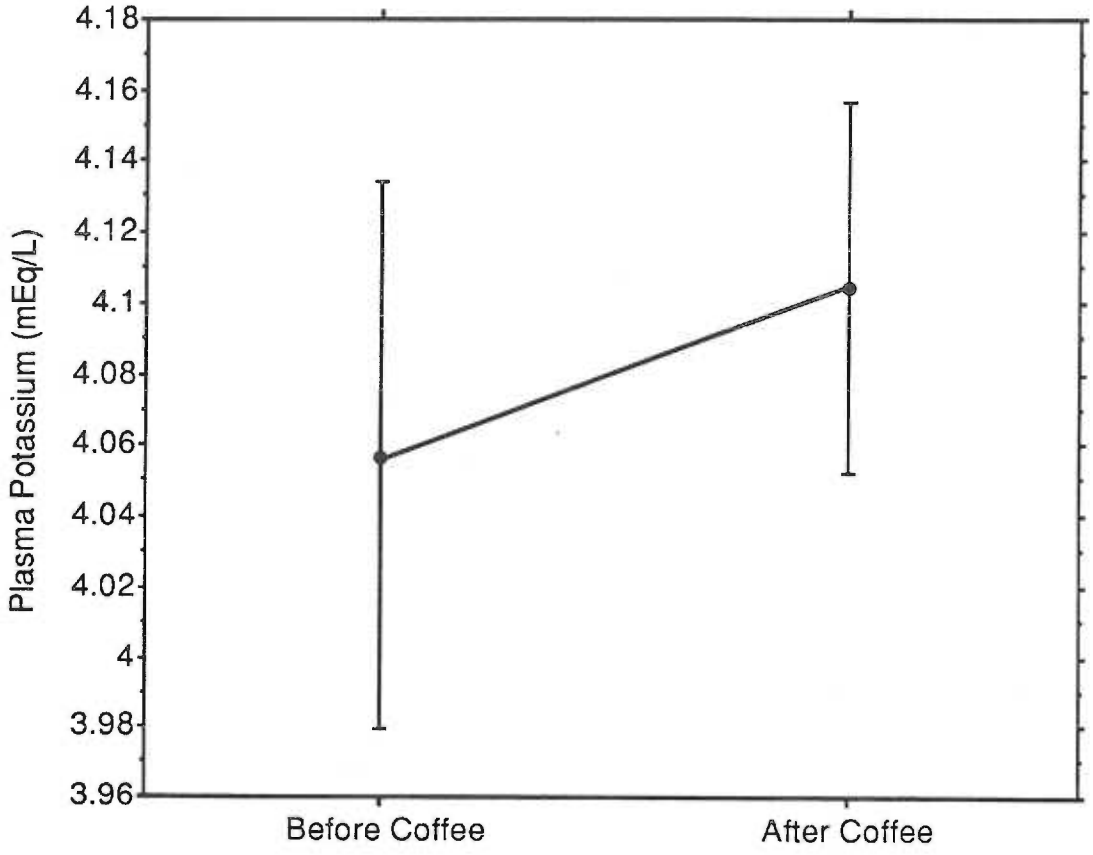

Figure 9. Mean plasma potassium values (±S.E.M.) before and after coffee.

Relationship Between Variables

The relationship between caffeine and catecholamine values are presented in Figure 10. No linear relationship exist between these two variables. Changes in catecholamine levels did not positively correlate with changes in caffeine levels.

Figure 11 describes the relationship between epinephrine and potassium levels. There is no linear relationship between the variables. It was expected that potassium values would decrease as epinephrine values increased.

The relationship between changes in severity and inducibility and caffeine values are presented in Figure 12. Positive changes in severity scores correlated with caffeine levels less than 7 mg/L and all negative changes in severity scores were associated with a caffeine levels greater than 5 mg/L. As caffeine levels increased, rhythms became more easily induced. The value of this is insignificant, since this induced group of rhythms includes noninducible and nonsustained rhythms.

Rationale for Data Analysis

Wilcoxon Summed Rank was selected for the data analysis procedure because it is a nonparametric method that measures two correlated samples having dependent ordinal variables. The severity and inducibility scores are representations of the electrophysiology data on an ordinal scale. The purpose of Wilcoxon Summed Rank is to test the difference in the ranks of scores of two related groups (Polit & Hungler, 1983). As presented in this research study, group one was the caffeine-free electrophysiology test and group two was the caffeine electrophysiology test. The Wilcoxon test assumes that the individual subjects who are measured twice are randomly and independently sampled.

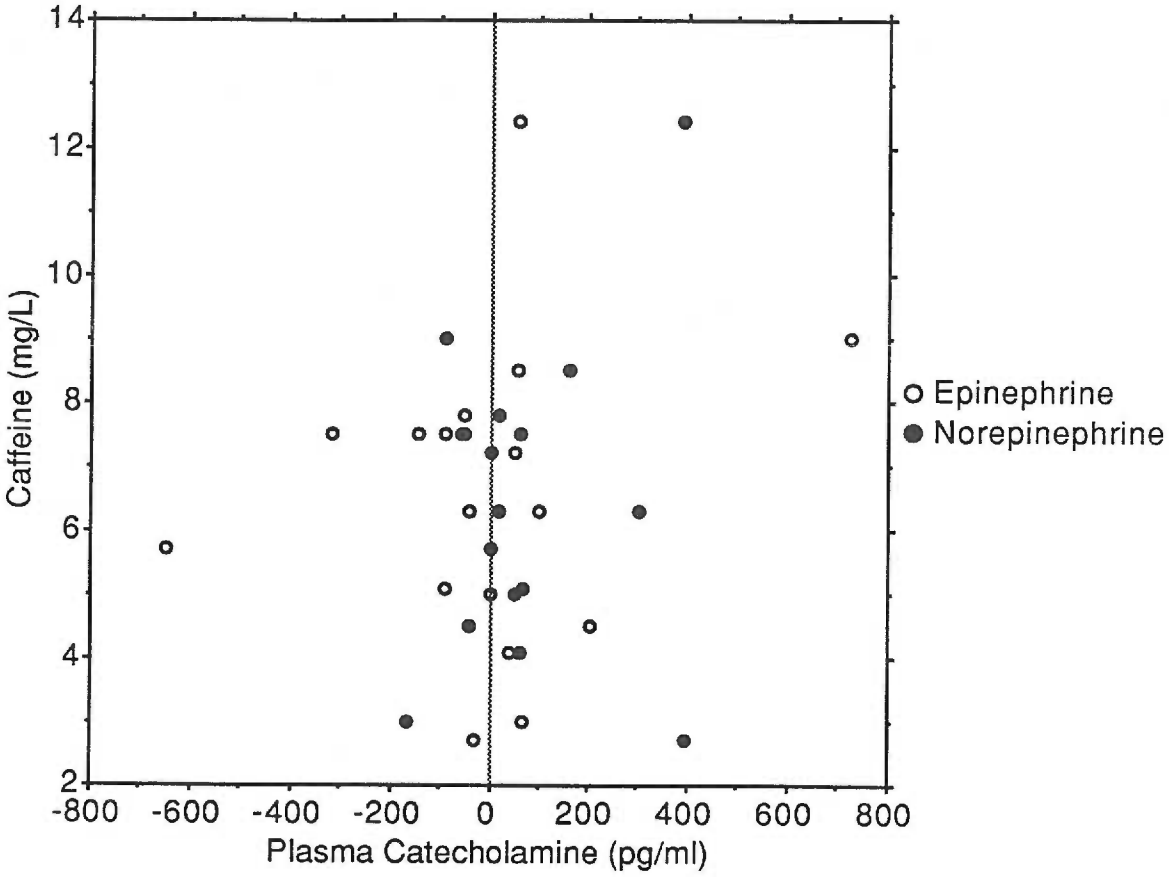

Figure 10. The relationship between plasma caffeine and changes in plasma catecholamine levels after 275 mg of caffeine.

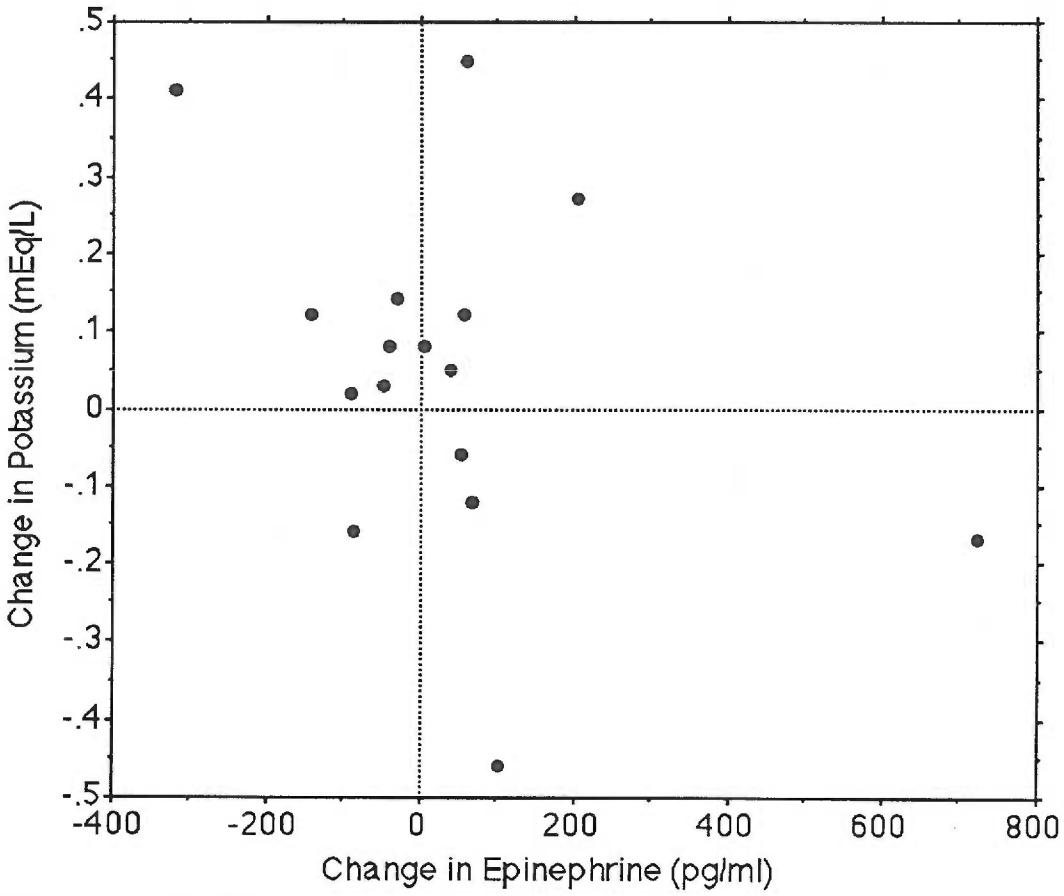

Figure 11. Relationship between changes in plasma potassium levels and plasma epinephrine levels after coffee.

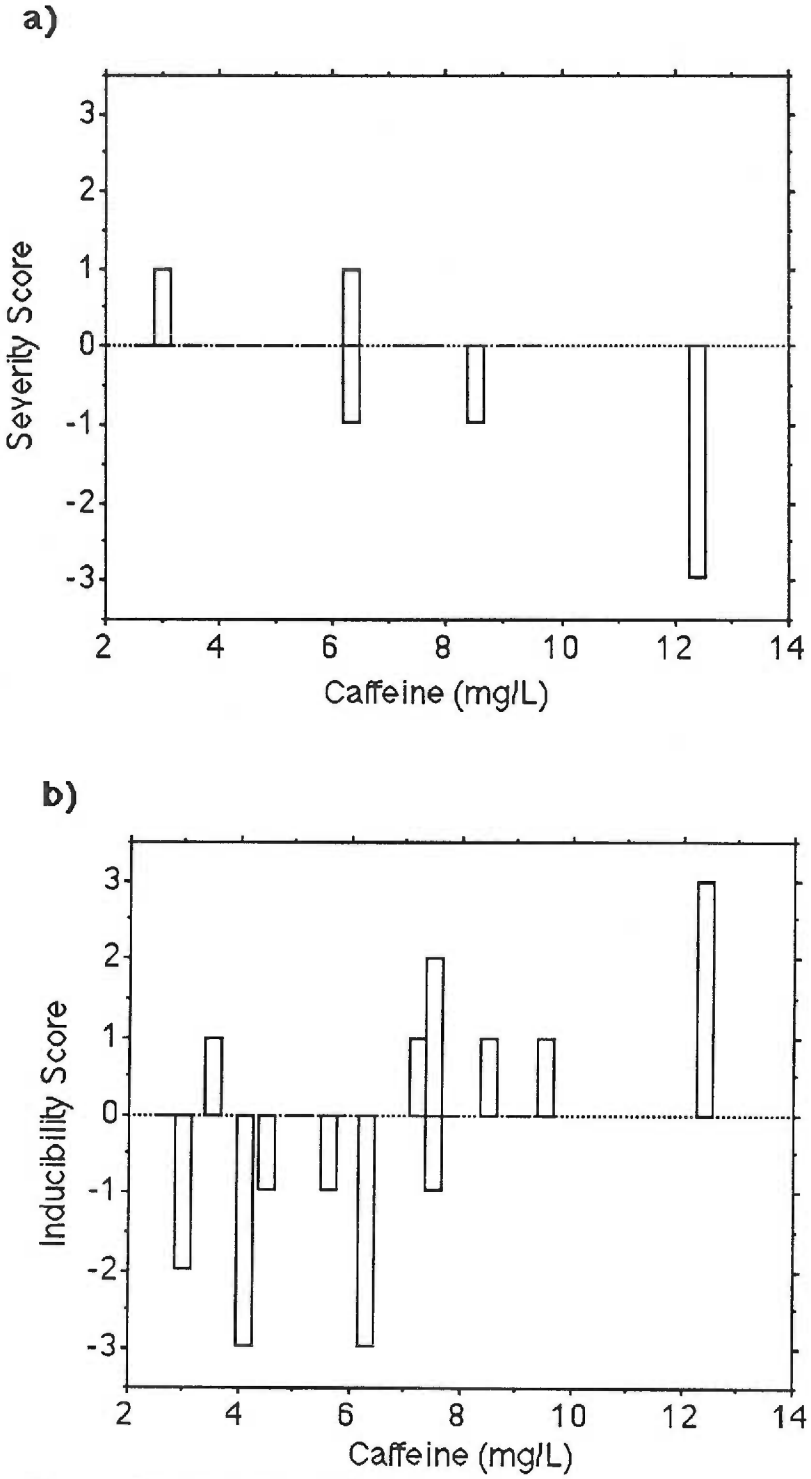

Figure 12. Relationship between plasma caffeine levels and a) severity and b) inducibility scores.

The null hypothesis for this type of data analysis is that the population distributions corresponding to the two sets of observation are the same. The alternative hypothesis states that the population distributions are not identical (McCall, 1986).

The Spearman's Rank order correlation was selected to determine the relationship between changes in potassium and catecholamine values (after caffeine) with ventricular arrhythmias (severity and inducibility). The purpose of this type of nonparametric data analysis is to test the existence of a correlation using at least ordinal scale measurements (Polit & Hungler, 1983). The null hypothesis states that there is no correlation and the alternative hypothesis states that a correlation does exist in the population. This type of test assumes that there are paired observations, and the subjects are randomly and independently sampled (McCall, 1986).

Paired t-test analysis was used to test the differences between two dependent group means using a ratio scale (Polit & Hungler, 1983). This parametric test was used to determine if there was a difference between the mean potassium and catecholamine values when measured before and after caffeine. The null hypothesis states that there is not a difference between the two group means. The alternative hypothesis supports that a difference exist between the means.

CHAPTER IV

Discussion

Arrhythmias after Caffeine

The effect of caffeine on severity and inducibility of ventricular arrhythmias was evaluated to determine if coffee consumption was safe for cardiac patients who had a history of these arrhythmias. Hypotheses one and two were not supported in this research study. Severity and inducibility of ventricular arrhythmias did not differ significantly between the subjects before and after caffeine.

Patient Sample

Degree of risk. The study sample consisted of 22 subjects with a clinical history of ventricular arrhythmias (77% of the group had either ventricular tachycardia or ventricular fibrillation). Coronary artery disease was present in 86% of the population, 64% had had a previous myocardial infarction, and 18% had a left ventricular aneurysm. Syncope with clinical arrhythmias was present among 64% of the subjects. Despite the risk factors for ventricular arrhythmias and hemodynamic instability, this group is considered a lower risk group than the general ventricular arrhythmia population. The degree of risk is less because 1) patients who required cardioversion during baseline testing were excluded from this study, and 2) 77% of the participating subjects had either noninducible (n=12) or nonsustained (n=5) ventricular arrhythmias during their baseline electrophysiology test. Prior researchers have noted that patients who have noninducible arrhythmias during an initial electrophysiology test will have a 95% survival rate at one year providing they have a high ejection fraction (>30%). The survival rate decreases to 75% if the ejection fraction is lower (Wilber et al., 1988). When patients are noninducible at baseline

electrophysiology testing, it is necessary to consider if other promoters of ventricular arrhythmias (e.g., ischemia, electrolyte abnormalities, or proarrhythmic effects of antiarrhythmic drugs) are the cause of the ventricular arrhythmia (Wellens et al., 1985). All subjects in this study had primary ventricular tachycardia or fibrillation at the time of entering in the study.

Age and gender. The percent of coronary events that present as sudden death increases with age (Rapaport, 1988). This study is representative of this fact with a large percentage (77%) of the sample being greater than 54 years of age. There were more males (91%) than females (9%) in the study population. The occurrence of CAD is known to be higher in men than women and hence a higher percentage of men are at risk for ventricular tachycardia. Although this study sample is not a homogeneous sample with respect to age and gender, it does represent the general population that is at highest risk for ventricular tachycardia.

Cardiac medications. All antiarrhythmic medications (excluding calcium channel blockers and digoxin) were held 36 hours prior to the study period. This time period allowed the serum levels of the antiarrhythmic medications to decrease by several half-lives before the caffeine study was initiated. Therefore, electrophysiology results were not influenced by drug therapy.

Coffee Consumption.

Habitual coffee drinkers. All subjects except one consumed greater than 100 mg of caffeine per day prior to their onset of ventricular arrhythmias. A 100 mg dose of caffeine is equal to approximately six ounces of percolated coffee or 4.5 ounces of brewed coffee. All subjects were chronic coffee drinkers prior to the onset of ventricular arrhythmias and hospital admission, but as they learned

about their ventricular arrhythmias, some (64% of the group) decreased their caffeine consumption.

Naive coffee drinkers (patients who do not consume coffee or other caffeinated beverages) were excluded from the study in an attempt to preserve a homogeneous group of patients who were tolerant to coffee and would have similar hemodynamic effects. Prior researchers indicated that hemodynamic responses to caffeine differ in naive versus habitual coffee drinkers (Robertson et al., 1981; Izzo et al., 1983). All subjects abstained from caffeine consumption at least 24 hours prior to the caffeine study. According to Robertson et al. (1981), greater than 24 hours of prior caffeine abstinence is necessary before maximal effects on blood pressure changes are noticed. It is unknown how much abstinence time is needed to see maximal caffeine effects on heart rhythms. It is possible that caffeine abstinence before acute caffeine ingestion has no effect on arrhythmias. The important reason to control caffeine intake prior to this study was to ensure that consistent caffeine levels and caffeine effects on arrhythmias, catecholamines and potassium could be achieved before and after caffeine.

Plasma caffeine levels and extraneous variables. Plasma caffeine levels obtained 15-120 minutes after 250 mg of caffeine had ranged from 3.8 to 14.8 mg/L (Robertson et al., 1978; Robertson et al., 1981; Izzo et al. 1983). One hour after 300 mg of caffeine, researchers obtained a mean caffeine value of 5.2 ± 0.2 mg/L (Myers et al., 1987). In the present study there was a wide range in plasma caffeine levels (2.7-12.4 mg/L). These variations could be due to 1) individual body mass, 2) individual peak caffeine times, or 3) medication (cimetidine).

The amount of caffeine that was administered to each subject was not standardized according to body weight. Each subject received the same amount of caffeine. The problem with administering caffeine in this manor is that plasma caffeine levels may vary due to differences in individual weights. The data collected from this study shows a non-linear relationship between the caffeine values and body mass indexes (figure 3). Therefore, weight alone did not influence the caffeine concentrations. Individual peak caffeine times and half-lives may have also influenced the obtained caffeine values. Some researchers (Sutherland et al., 1985; Newcombe et al., 1988) controlled for these variables, but their method for measuring arrhythmias was long-term ambulatory monitoring. With electrophysiology testing, the method for administering coffee was acceptable since acute effects of caffeine were evaluated rather than long term effects.

The high plasma caffeine value (12.4 mg/L) in subject #14 may have been due to the cimetidine that this patient was taking during the study period. Cimetidine is known to reduce the hepatic metabolism of caffeine, thus decreasing the rate of elimination from the blood. It is not clear if the cimetidine received by this subject had truly influenced the caffeine level since the half-life of this medication is two hours. The last dose of cimetidine given to this patient was 17 hours before the caffeine test. The lower caffeine levels (2.7-3.0) in other patients may have resulted from measurement of plasma levels prior to or after the peak time. The plasma caffeine levels in this study were measured 35 (n=1), 45 (n=13), 50 (n=4) and 60 (n=4) minutes after completion of coffee. The caffeine level measured at 35 minutes after consuming coffee was 5.0 mg/L. The caffeine level of 2.7 was measured 60 minutes after consumption.

Coffee ingestion has a greater effect on the blood pressure and heart rate in older individuals (>50 years) than younger individuals (<30 years) (Izzo et al., 1983). It is unknown if this is true with heart rhythms. With the present study, there was a wide age range (39-72 years). Both age groups (>50 years, <50 years) had varying responses to caffeine in terms of severity and inducibility after caffeine ingestion (see below). Plasma caffeine levels varied widely with age but there was no difference in mean values. The mean plasma caffeine level for subjects less than 50 years of age was 6.1 mg/L and for subjects greater than 51 years it was 6.2 mg/L.

Individual Circadian Patterns.

Researchers have shown that circadian variability exists with measurements of ventricular ectopy by long-term ambulatory monitoring (Lown et al., 1973; Orth-Gomer et al., 1982; Yanaga et al., 1982; Nademanee et al., 1989) . It is unclear if this type of variability exists with programmed ventricular stimulation (electrophysiology testing). In this study, circadian variation of rhythm inducibility, plasma catecholamine and potassium levels was not controlled because it would have interfered with the electrophysiology scheduling of these patients. This investigator had no control over the schedule. All subjects except one had a day awakening and night sleeping schedule. That subject's caffeine-free test took place at 1700 during his customary late sleeping hours. Other day subjects were tested during various hours: 0700-1000 (n= 9), 1001-1400 (n=5), and 1401-1800 (n=7). Positive changes in severity scores (revised scores) occurred during the hours of 0700-1000 (n=1) and 1401-1800 (n=1). Negative changes occurred between 0700-1001 (n=1) and 1401-1800 (n=2). The number of subjects is too small to show if a circadian pattern of caffeine induced arrhythmias exist.

Figure 13 shows the relationship between rhythm scores and hours after waking for each individual. Positive changes in severity scores were noted at one and ten hours after waking. These times are consistent with prior research in relation to increased ectopy (Lown et al., 1973; Orth-Gomer et al., 1982; Yanaga et al., 1982; Nademanee et al., 1989). Positive changes in inducibility scores occurred during the early and late hours after waking.

Severity Scores

Less severe arrhythmias. With the revised scoring system, three (14%) subjects had less severe arrhythmias after caffeine ingestion. Two subjects changed from nonsustained VT to noninducible arrhythmias (less than four beats of repetitive PVBs) after caffeine. One subject with sustained VT during baseline was not inducible during the caffeine electrophysiology test. This particular subject (#14) developed sustained VT after additional stimuli were added to the standard electrophysiology protocol.

More severe arrhythmias. With either the Kudenchuk et al. (1986) arrhythmia scoring system or the revised scoring system, two (9%) of the subjects had more severe arrhythmias after coffee. These subjects had noninducible rhythms during the caffeine-free test and nonsustained VT during the caffeine test.

Electrophysiology testing after caffeine has been evaluated by only one other group of researchers. Dobmeyer et al. (1983) also noted that patients (2/12) who were noninducible at baseline had nonsustained VT following 200 mg of caffeine. They also found a significant shortening of the effective refractory period of the right ventricle. These patients had a history of heart disease, but no previous documentation of ventricular tachycardia.

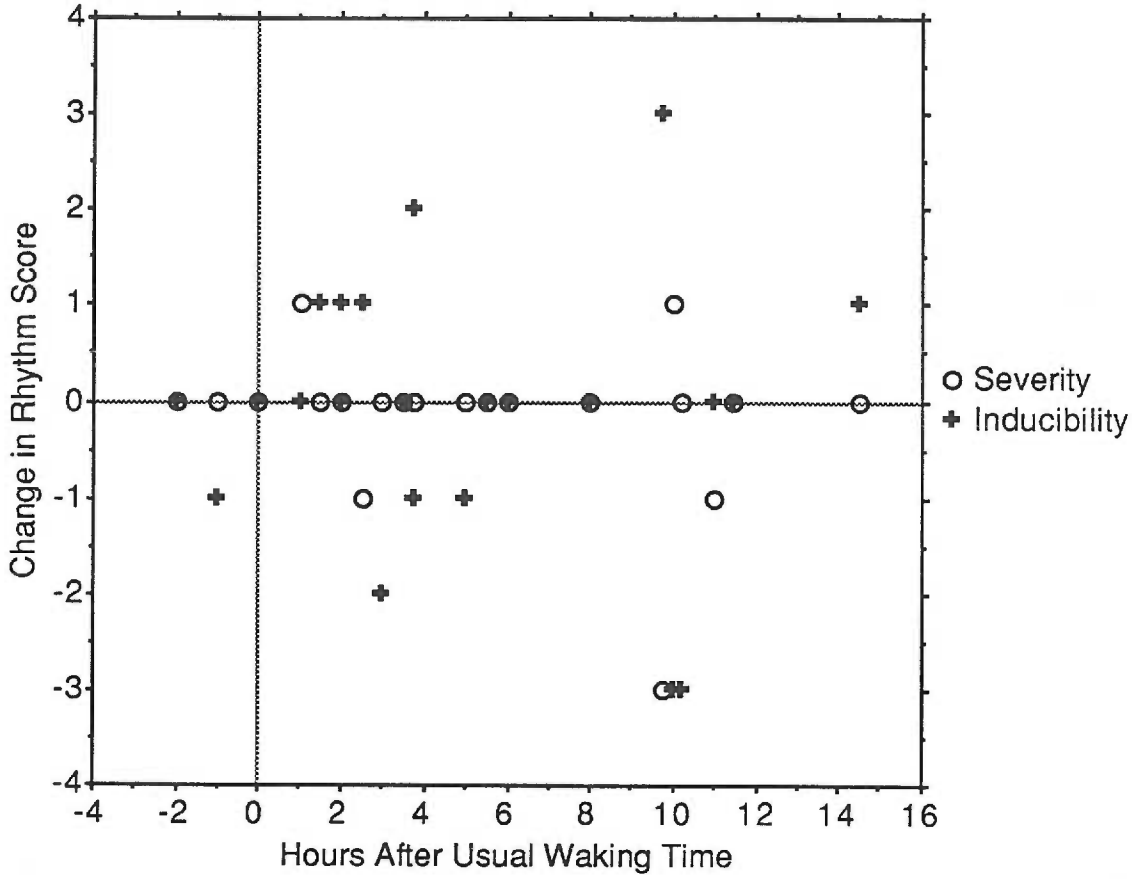

Figure 13. The relationship between hours after usual waking time and change in rhythm scores (revised severity scores).

Previous electrocardiographic (Holter) monitoring studies show that a serving of coffee with 250-300 mg/L of caffeine does not significantly change the frequency or severity of ventricular arrhythmias (Myers et al.,1987; Myers & Harris, 1988; Newcombe et al., 1988). As the milligrams of caffeine increased from 450 to 900 mg per day (Harris et al., 1989), the severity and frequency of ventricular arrhythmias was shown to increase. With electrophysiology testing, Dobmeyer et al. (1983) showed that severity of ventricular arrhythmias increased with only 200 mg of caffeine in cardiac patients with a history of palpitations. Electrophysiology testing may be more sensitive in detecting changes in the cardiac substrate with lower doses of caffeine than Holter monitoring. Cardiac substrate, in relation to VT, is defined as myocardial tissue with uneven refactory and conduction characteristics.

Sustained ventricular tachycardia. Three out of the five subjects who had sustained ventricular tachycardia during a caffeine-free test had a faster VT rate after caffeine. The rate of VT increased 20 to 30 bpm from the baseline VT rate in these subjects. The changes in VT rates were not measurable with the Kudenchuk or the revised scoring system. One subject had no change in VT rate after caffeine, while another subject with sustained VT during baseline was not inducible during the caffeine electrophysiology test (as explained above). This subject had sustained VT (10 bpm faster) after additional electrophysiology stimulation.

Prior research has demonstrated that the rate of supraventricular tachycardias can be made to increase (cycle length decreased from 345 ± 44 to 321 ± 44 msec) by infusing epinephrine (25-50 ng/kg/min) intravenously. A cycle length is a measure of RR interval on electrocardiogram. The mechanism of this acceleration is felt to be secondary to the effect of epinephrine on the

sinus node, AV node and other atrial conduction tissue (Morady et al., 1989). It is interesting to speculate that the increased rate of VT seen during the caffeine electrophysiology test is secondary to caffeine's effect (direct or indirect) on the ventricular conduction tissues maintaining the tachycardia. It is tempting to extrapolate from this study and hypothesize why some patients who have inducible ventricular arrhythmias at baseline might not be inducible after caffeine. If the the conduction time through only certain areas of the tachycardia re-entry loop are altered, then the impulse might arrive at a region only to find that it is now refractory (having depolarized relatively earlier) and unable to maintain the tachycardia circuit.

Inducibility Scores

Evaluation of ventricular arrhythmia inducibility was done with a scoring system developed by the researcher. The ease of inducibility of VT did not change significantly after caffeine ingestion. This suggests that caffeine does not effect the ease of rhythm induction. These data are difficult to interpret because the significance of changes in the number of extrastimuli used to induce a noninduced or nonsustained rhythm is not well defined in the literature. With the induction of sustained VT, researchers believe that the use of three and four extrastimuli versus one or two extrastimuli demonstrates the rhythm is harder to induce (Wellens et al., 1985) and the reproducibility is lower (Kudenchuk et al., 1986).

The number of extrastimuli needed to induce ventricular arrhythmias (including 0-3 repetitive PVB) after caffeine increased in six (27%) and decreased in six (27%) subjects. The change in number of extrastimuli used for noninducible rhythms does not reflect clinical importance. Therefore, further

discussion of inducibility refers only to four subjects who had inducible sustained VT before and after caffeine.

The number of extrastimuli required to induced VT after caffeine in these subjects were unchanged in two (50%) and decreased in two (50%) patients. Caffeine increased the ease of VT induction in two patients (#5,21). These two male patients also had faster VT rates after caffeine. Their ages were 39 and 43 years and they both had a history of CAD and clinical sustained VT. Their caffeine levels were 7.0 and 7.2 mg/L. Plasma catecholamine values increased in subject #5 and decreased in subject.# 21. Plasma potassium decreased in subject #5 and increased in subject #21. Blood samples from subject #21 may be inaccurate due to venipuncture, time of venipuncture and delayed laboratory transfer time. The two male subjects who had unchanged inducibility scores both had a history of CAD and documented VT. They were 67 and 62 years in age. Their caffeine levels were 5.0 and 2.7 mg/L. Possibly, if the 2.7 mg/L caffeine level had been higher, then this subject (who had unchanged sustained VT rate and inducibility score) might have had a faster or more easily induced sustained VT.

Description of Subjects and Laboratory Measurements in Relation to Severity and Inducibility

No change in severity or inducibility scores after caffeine. Eight subjects, aged 48-68 years, had baseline ventricular arrhythmias that did not change after consuming coffee. Their clinical rhythms were nonsustained VT (n=3), sustained VT (n=3) and ventricular fibrillation (n=2). These subjects had caffeine levels that ranged from 2.7 to 9.0 mg/L. Potassium levels declined in two and increased in six subjects. Epinephrine values increased in two and declined in six subjects. Norepinephrine values increased in six subjects. The

changes in plasma potassium and epinephrine values are not consistent with the theory that supports ventricular arrhythmogenesis since potassium levels would have been expected to decrease and catecholamine levels would be expected to increase. Therefore, it is understandable why these subjects did not have worsening of their baseline electrophysiology test results after caffeine. Since a majority(6/8) of subjects had elevated norepinephrine levels after caffeine, it is probable that increasing norepinephrine levels were not proarrhythmic in this patient group.

Positive change in severity score after caffeine. Two subjects who had more severe ventricular arrhythmias after caffeine. Subject #2 (see Table 7) had noninducible rhythms at baseline and nonsustained VT after caffeine. Inducibility was unchanged. Subject #18 had noninducible rhythms at baseline and nonsustained VT with a negative change in inducibility after caffeine. Both subjects were male and 70 and 69 years of age, respectively. Their clinical rhythms were VT and ventricular fibrillation. They had caffeine levels of 3.0 to 6.3 mg/L. Their plasma potassium levels decreased and epinephrine levels increased after caffeine. Subject #2 had a decreased in norepinephrine level and subject #18 had an increase in this value. Both subjects had a history of CAD, and subject #2 also had a left ventricular aneurysm. These two subjects who had increased arrhythmias severity had potassium and epinephrine levels that were consistent with the theory that supports arrhythmogenesis.

Negative changes in severity scores after caffeine. There were three subjects who had less severe ventricular arrhythmias after caffeine. Subject #3 had a noninducible rhythm and no change in inducibility score; subject #6 and #14 had noninducible rhythms and a positive changes in inducibility scores after consuming coffee (see Table 7 for baseline rhythms). All subjects were

male and 48 to 72 years of age. All the clinical rhythms were nonsustained VT and sustained VT. They had caffeine levels of 6.3 to 12.4 mg/L. After coffee, plasma potassium levels increased in all subjects. Epinephrine levels increased in two and decreased in one subject and norepinephrine levels increased in all subjects . All subjects had a history of CAD, and subject #14 also had a history of congestive heart failure and chronic renal insufficiency. Increased potassium values in these subjects with decreased severity is consistent with the theory that supports this study. Positive (increased) changes in potassium were associated with no change in severity scores, but positive potassium changes were not associated with positive changes in severity scores.

Atrial Arrhythmias.

A history of atrial arrhythmias was present in 27% of the subjects prior to this study. Despite this large percentage, atrial arrhythmias did not occur in any subjects during the caffeine-free or caffeine test. The electrophysiology tests were limited to programmed ventricular stimulation only.

Electrophysiology versus Holter Monitoring

Holter monitoring is a method that is used to evaluate efficacy of antiarrhythmic agents on the triggering mechanism, which may be a prerequisite for the initiation of tachycardia due to re-entry or increased automaticity. Electrophysiology testing is a measurement of induction of VT. The mode of induction is dependent on the nature (refractory period and conduction velocities) of the diseased tissue that is the substrate for potential reentry, the distance and conduction time from the stimulation site to the potential reentry circuit, and the refractory periods of the local myocardium at the stimulation site (Kim, 1989). Information related to the effects of caffeine on

ventricular ectopy (Holter monitoring) is plentiful, but little is know about how caffeine affects the substrate in relation to induction of ventricular arrhythmias (electrophysiology testing).

When measuring ventricular tachycardias by Holter monitoring, one must be cautious of the poor reproducibility of this tool. Evaluation of arrhythmia severity and frequency (ventricular ectopy or VT) with this tool is weakened by the large variability of day to day reproducibility. To determine efficacy of a therapy with Holter monitoring, it is necessary to obtain several days of monitoring. The reproducibility of this method increases as the monitoring time increases (Morganroth et al, 1978; Michelson et al., 1981). Many of the existing caffeine studies used Holter monitoring. The validity of these studies should be questioned if only short term single readings were done.

The reproducibility of electrophysiology testing is 73-97% when using a protocol with four extrastimuli. Nonrepoducibility increases as the number of extrastimuli required to induce a rhythm increases from one to four (Kudenchuk et al., 1986). Electrophysiology testing is a more sensitive test than Holter monitoring (Kim, 1989).

Conclusion: Arrhythmias After Caffeine.

The effect of caffeine on ventricular arrhythmias has been evaluated in normal subjects (Prineas et al., 1980; Newburg, 1984; Sutherland et al., 1985; Newcombe et al., 1988) and subjects with heart disease (Dobmeyer et al., 1983; Myers et al., 1987; Schneider, 1987; Myers & Harris, 1988; Harris et al., 1989). The important question asked in this study is whether caffeine increases the severity or ease in inducibility of ventricular tachycardias in cardiac patients who have a history of ventricular arrhythmias. Subjects with ventricular ectopy were evaluated by Dobmeyer et al. (1983) and Sutherland et al. (1985). Harris

et al. (1989) studied subjects who had organic heart disease and ventricular arrhythmias, but subjects with sustained ventricular tachycardia were excluded. This current study evaluates a higher risk population because it includes those patients with sustained ventricular tachycardia.

Patients who are at highest risk for sudden cardiac death, according to Rapaport (1988), are those who are survivors of myocardial infarction with left ventricular dysfunction and/or complex ventricular ectopy; survivors of out-of-hospital cardiac arrest when not associated with an acute myocardial infarction; patients with recurrent ventricular tachycardia; and patients with dilated congestive cardiomyopathy, particularly when associated with ventricular ectopy. These patients who are at increased risk for sudden cardiac death may also be at increased risk for caffeine induced arrhythmias.

This study demonstrates that not all patients from this patient sample have increased severity or inducibility of ventricular arrhythmias after 275 mg of caffeine in coffee form. This study sample is not a high risk group, but some subjects may have been at a higher risk for sudden death than others. Five patients had increased severity (positive change with the revised scoring system or increased VT rate) and two of these patients had increased ease of inducibility (subjects with sustained VT before and after caffeine). It is unknown if these patients represent a select population of caffeine "sensitive" individuals, and what characteristics define them as such.

This male patient group (patients with increased severity) had a history of CAD with prior myocardial infarction and clinical sustained VT(n=3) or ventricular fibrillation(n=2). A history of left ventricular aneurysm and congestive heart failure was present in three of these subjects. Ejection fractions from three patients were 0.15, 0.22, and 0.35. Their caffeine levels

ranged from 3.0 to 7.5 after the 275 mg serving of caffeine. Prior to hospitalization, three patients consumed 100 mg or less of caffeine per day; one consumed 100 to 400 mg; and one consumed greater than 400 mg per day. Three other subjects who had non-sustained VT before and after caffeine also had a history of left ventricular aneurysm.

The coronary heart disease and reduced ejection fraction seen in these patients may be characteristics that led to increased severity and/or increased ease in inducibility of arrhythmias after coffee. The difference in the underlying substrate of these five patients may account for their differing responsiveness to electrophysiology testing after caffeine.

Plasma Catecholamine Concentrations after Coffee

The relationship between increased plasma epinephrine and norepinephrine levels and ventricular arrhythmias was evaluated in cardiac patients after consumption of coffee. There was no significant correlation between plasma catecholamine and increased severity and inducibility of ventricular arrhythmias. Hypotheses three and four were not supported in this research study.

Previous Research

Myers et al. (1987) measured plasma catecholamine levels after 300 mg of caffeine and found that plasma epinephrine increased from 58 ± 4 pg/ml to 88 ± 6 pg/ml three hours after caffeine ingestion. Changes in plasma norepinephrine levels were not significant; they changed from a mean of 310 ± 15 to 325 ± 30 pg/ml at three hours after caffeine ingestion. The severity of arrhythmias measured by Holter monitor did not increase in these patients after caffeine despite the significant change in the mean plasma epinephrine level.

Morady et al. (1988) demonstrated that increased plasma epinephrine concentrations can induce sustained ventricular tachycardia via electrophysiology testing. Sustained ventricular tachycardia occurred in 3/20 subjects who had no prior history of this arrhythmia. Arrhythmia inducibility become easier with elevated epinephrine levels. They achieved significant elevations in plasma epinephrine and norepinephrine levels (862 ± 226 S.D. pg/ml and 503 ± 218 S.D. pg/ml, respectively) after infusion of epinephrine 25 ng/kg per minute. Norepinephrine elevations were thought to be related to endogenous secretions.

Other researchers have shown that the mean plasma epinephrine level peaked to 89 ± 12 pg/ml (SEM) one hour after caffeine and the mean plasma norepinephrine level peaked to 238 ± 17 pg/ml (SEM) three hours after 250 mg of caffeine. These values were considered significant changes within one to three hours from baseline values for both epinephrine and norepinephrine (Robertson et al., 1978). A further study showed a peak mean epinephrine value of 100 pg/ml and a peak mean norepinephrine value of 470 pg/ml three hours after 250 mg of caffeine (Robertson et al., 1981).

Epinephrine and norepinephrine levels from this caffeine study were high in comparison to other caffeine researchers. The epinephrine values changed from a mean value of 401.2 ± 108.5 to 394.6 ± 82.7 (SEM) pg/ml after caffeine consumption. Plasma norepinephrine levels increased from a mean value of 559.2 ± 65.1 to 625.3 ± 69.1(SEM) pg/ml.

Dimsdale and Moss (1980) stated that epinephrine rises are characteristic of psychological stressors and norepinephrine rises are in response to physical stressors. They demonstrated in nine subjects that mean plasma epinephrine level after public speaking increased to 336 pg/ml and the mean plasma

norepinephrine level after physical exercise increased to 1942 pg/ml. Norepinephrine also increased after public speaking, but the changes were less significant than epinephrine changes (mean value was 919 pg/ml). The difference between epinephrine and norepinephrine values obtained from prior researchers and from this caffeine study may be due to the psychological stress of electrophysiology testing. The first mean epinephrine value (before coffee) may have been higher than the second mean epinephrine value (after coffee) because the patients were anticipating their first electrophysiology test in the CCU (new setting) instead of the catheterization laboratory. The epinephrine levels obtained in this caffeine study are similar to those obtained by Dimsdale and Moss (1980) after public speaking. Norepinephrine levels are comparable to those obtained by Morady et al. (1988) after epinephrine infusion during electrophsiology testing. The stress induced from electrophysiology testing may have masked the effects of caffeine on catecholamine concentrations.

Myers et al. (1987) used four hours of Holter monitoring to measure ventricular ectopy in the hospital setting. Physical activity levels were not discussed during this study. Holter monitoring is most likely less stressful than electrophysiology testing. Therefore, high epinephrine levels were not observed by those researchers as they were in this caffeine study.

Variation of Catecholamine levels

There are large variations in the catecholamine measurements from this study. Some reasons exist for these variations. First, the sample population is small. As the number of subjects increase, the variation from the mean value will decrease. Second, this type of specimen is easily influenced by variables that cause the catecholamine values to change rapidly. These variables are sympathoadrenal stimulation and laboratory techniques.

Sympathoadrenal stimulation. Catecholamine values are difficult to measure because the half-life is approximately three minutes and the levels fluctuate in a matter of seconds in response to sympathetic stimulation (Dimsdale & Moss, 1980). Fluctuations in values occur in response to physical activity, emotional stressors, and diet (Robertson et al., 1979). Venipuncture is an emotional stressor for some patients and it can greatly alter epinephrine values (Carruthers et al., 1970).

Subject #22 had an indwelling catheter placed 45 minutes prior to collection of baseline specimens. This patient had a positive change in epinephrine levels and a negative change in norepinephrine. The epinephrine value may have been falsely elevated.

As stated before, 27% of the sample population had venipuncture blood sampling before and after caffeine. In this group of patients (n=6), the mean plasma epinephrine before coffee was 592 pg/ml and after coffee was 474.3 pg/ml. Both of these values are higher than the total group mean values. The mean plasma epinephrine levels prior to coffee in the nonvenipuncture group (n=10), excluding #22, was 270.9 pg/ml and after coffee was 310 pg/ml. There was no significant difference between the mean epinephrine values of the venipuncture and nonvenipuncture groups ($p>0.05$) as tested by T-test analysis.

Laboratory techniques. Delayed freezing of plasma epinephrine and norepinephrine samples can alter the concentration of these hormones. Catecholamines in plasma are destroyed by enzymes monoamine oxidase and catechol-o-methyltransferase. To prevent this destruction, blood samples need to be centrifuged and frozen immediately. The concentration of catecholamines decreases nearly 25% after 12 minutes at room temperature (Carruthers et al., 1970). In this caffeine study, all catecholamine samples were placed

immediately in an ice bath, but transfer time to the laboratory was delayed (greater than 15 minutes) for two samples. Some values may have been falsely low due to the lack of a refrigeration type of centrifuge for four samples. These four samples had lower mean catecholamine values when compared to the group mean values (epinephrine and norepinephrine before = 147.7 & 459.1 pg/ml; epinephrine and norepinephrine after = 319.3 & 554.8 pg/ml).

The lack of significant changes in plasma catecholamine levels in this caffeine study may have also been due to the timing of catecholamine specimen collection. Specimens were collected 45-60 minutes after completion of coffee beverage. This collection time may have been too early for peak catecholamine levels to be achieved. Other researchers demonstrated that peak plasma catecholamines occurred between one and three hours after caffeine (Robertson et al., 1978, 1981). Significant variability exists in the timing of peak plasma catecholamine levels after caffeine. Some researchers were unable to obtain a peak plasma level or demonstrate a significant change in levels within three hours after caffeine (Izzo et al, 1983).

The reliability of catecholamine measurements are indicated by coefficients of variation (Goldstein et al., 1981). The measurements obtained from this study had larger intra-assay variability when compared to the coefficient of variation. This demonstrates that the catecholamine values may not be reliable because they had poor reproducibility. It is important to remember that only six samples were measured for intra-assay variability and that reproducibility of catecholamine concentrations are difficult to produce due to normal variations in the measurements. Coefficient of variations is normally 10-12% for epinephrine and norepinephrine respectively, but lower values 7.1 and 4.1% were calculated for this study's assay set-up.

Catecholamine and Extraneous Variables

Age. Epinephrine levels were seen to be higher in younger subjects (<30 years) and lower in older subjects (>50 years) (Izzo et al., 1983). In this caffeine study, the mean epinephrine values after caffeine were different. They were higher in subjects greater than 50 years (428.5 pg/ml) and lower in subjects less than 50 years (313 pg/ml). These values from this caffeine study can not be directly related to the study by Izzo et al. (1983) because the age groups are different and the age range is skewed with only five subjects less than 50 years of age.

Circadian periodicity. Catecholamine concentrations are known to elevate prior to and during early waking hours (Muller, Tofler & Stone, 1989). Therefore, higher concentrations of catecholamines would be expected from those subjects with early specimen collection times (two hours before and six to eight hours after awakening). Figure 14 demonstrates that there is no clear relationship between change in epinephrine values and time after waking when plasma specimens were collected. But more positive than negative norepinephrine changes did occur during the early specimen collection time. Individual specimens (before and after coffee) may have been influenced by circadian rhythms, but the changes in these catecholamine concentrations was not obviously influenced. There was an average of two hours between plasma collection times. It is difficult to expect a circadian pattern of catecholamine concentrations to be apparent here because of quick fluctuations in these levels and the small number of samples that were measured.

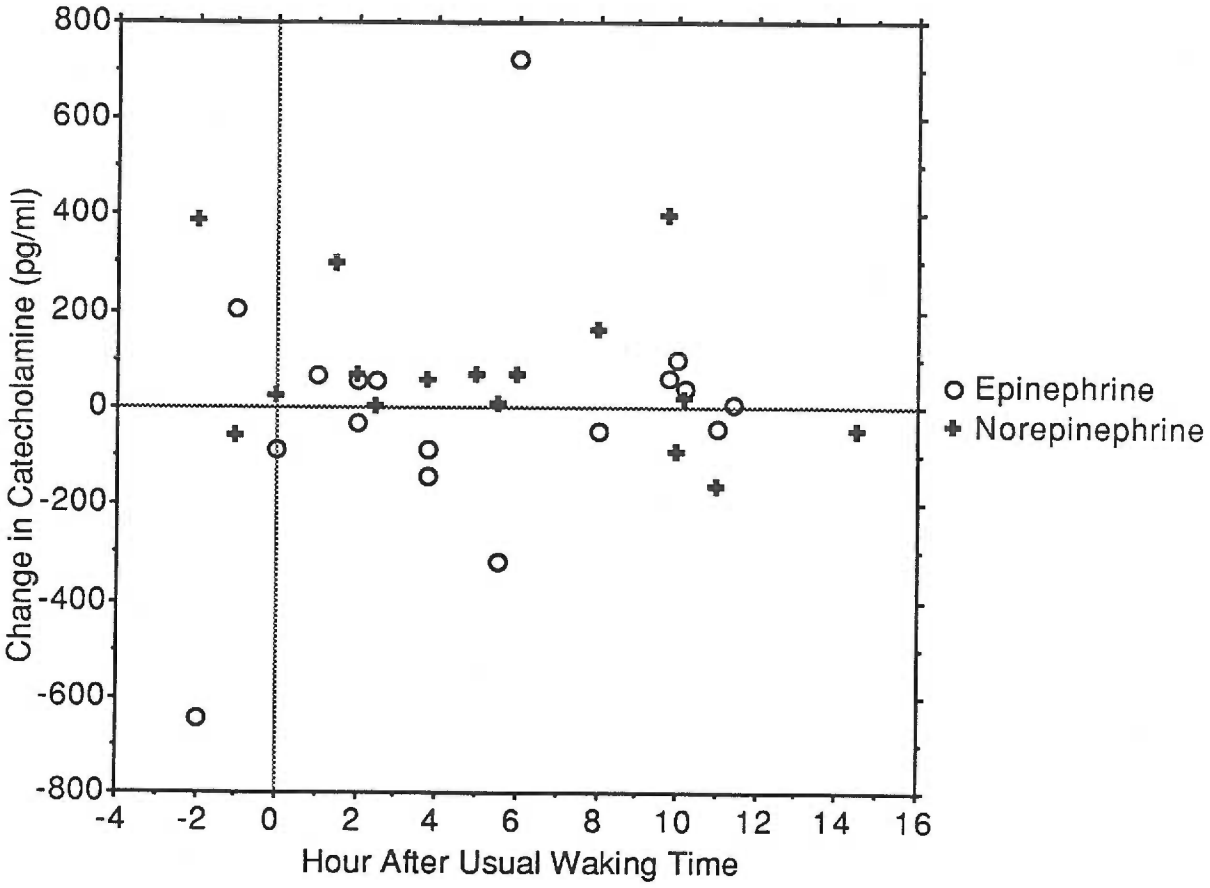

Figure 14. The relationship between hours after usual waking time and changes in plasma catecholamine levels.

Plasma caffeine concentrations. It would be reasonable to suspect that plasma catecholamine levels should increase as plasma caffeine levels increased. This relationship does not exist for this caffeine study as described by the scattergram (figure 10). Little information can be found in the literature that supports this relationship. This lack of correlation may be a result of the extreme variations in the plasma catecholamine concentrations.

Conclusion

Other researchers have demonstrated that caffeine intake can increase catecholamines, but this study does not strongly support catecholamine increases. The mean norepinephrine value did approach statistical significance. Because of the lack of correlation between catecholamine concentrations and severity and inducibility of ventricular arrhythmias, it is thought that caffeine's effect on arrhythmias could possibly be related to other indirect effects such as the prolonged cAMP effect within the cell. Further research is needed to determine this.

Plasma Potassium Concentrations after Coffee

The relationship between plasma potassium levels and ventricular arrhythmias was evaluated in cardiac patients after consumption of coffee. There was no significant correlation between plasma potassium levels and increased severity and inducibility of ventricular arrhythmias. Hypotheses five and six were not supported in this research study.

Previous Research

The relationship between plasma potassium and caffeine ingestion has not been described by other researchers. It was suspected that plasma potassium levels would decrease after coffee based on the knowledge that potassium ion influx occurs after high endogenous catecholamine secretions (Karlsberg et al.,

1981; Morgan & Young, 1982; Sutherland et al., 1983). Hypokalemia is induced by stimulation of B1 and B2 receptors when associated with high epinephrine concentrations (Brown et al., 1983; Struthers et al., 1983; Bia et al., 1986; Reid et al., 1986).

Mean plasma potassium levels in the present study did not change after caffeine ingestion possibly because of the following reasons. 1) The mean plasma epinephrine level did not increase significantly following caffeine ingestion, and hence the expected epinephrine effect on mean plasma potassium levels did not materialize. 2) Coffee contains a small amount of potassium (11 mEq per serving of coffee used for this study) which may have prevented a decline in mean potassium levels. 3) Lysis of red blood cells in the potassium blood sample prior to extraction of plasma by centrifugation may have artificially elevated potassium levels. 4) Laboratory errors occurred such as: prolonged transfer time before specimens were centrifuged (n=3); specimen placed in ice bath (n=1); and specimen obtained by venipuncture (n=6). These laboratory errors may have falsely elevated four results and decreased six values. 5) The changes in plasma potassium were measured at various times of the day and circadian rhythms may have influenced their levels. As figure 15 shows, there is no correlation between hour after waking and change in potassium level. The scattergram shows no linear relationship.

Conclusion

Other researchers have determined that potassium concentrations decrease as a result of elevated epinephrine. This study does not strongly support this relationship because mean epinephrine values did not increase above basline values and potassium replacement may have occured secondary to the potassium content in coffee itself.

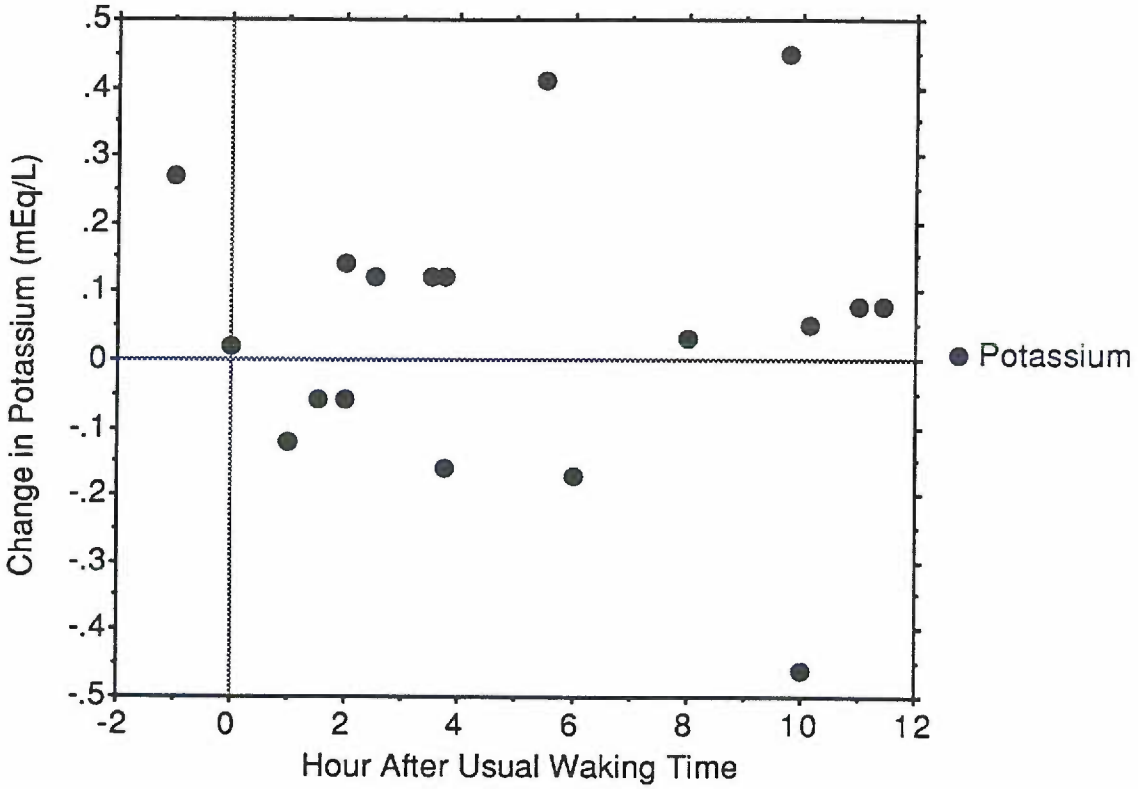

Figure 15. The relationship between hour after usual waking time and changes in plasma potassium levels.

CHAPTER V

Summary

This study was conducted to determine if coffee ingestion is safe for cardiac patients who have a history of ventricular arrhythmias. Coffee ingestion had been evaluated previously in patients with a history of palpitation, ventricular ectopy, and nonsustained VT, but never in patients who had prior sustained VT or ventricular fibrillation. Furthermore, the effects of caffeine on ventricular arrhythmias had been assessed with electrophysiologic testing by only one other research group looking at "normals" as well as a cardiac disease population (consisting largely of patients with mitral valve prolapse). Other researchers, using electrocardiographic measurements (Holter monitoring) found various results in frequency and severity of ventricular ectopy when assessed after caffeine ingestion. The variability in the results obtained stems from the type of subjects evaluated, the amount of caffeine administered, and the type of measurement tool used.

In the present study, coffee containing 275 mg of caffeine, was served to 22 subjects with heart disease (mostly CAD) who had previously experienced ventricular arrhythmias (nonsustained VT, sustained VT, ventricular fibrillation). One hour after the coffee was consumed, an electrophysiology study was performed and caffeine, catecholamine and potassium levels were measured. There was no significant difference in ventricular arrhythmias when measured before and after caffeine. Nine percent of the study population had more severe ventricular arrhythmias while fourteen percent had less severe ventricular arrhythmias after caffeine. Three out of five patients who had VT at baseline had faster VT rates following caffeine. Two out of four patients who had VT during the caffeine-free test had more easily induced VT after caffeine.

Although, caffeine did not statistically influence ventricular arrhythmias in this patient population, there is concern regarding the increased severity and inducibility of these rhythms in some patients. The characteristics of these patients (those who had increased severity scores, increased inducibility scores with VT , faster VT rates,) are the following: male gender; coronary artery disease with previous myocardial infarction; clinical VT or ventricular fibrillation; left ventricular aneurysm and congestive heart failure in three patients; and low ejection fractions (0.15, 0.22, 0.35).

In conclusion, it is suggested that caffeine ingestion be limited in patients with a history of ventricular tachycardia and ventricular fibrillation. Although arbitrary, it is recommended that caffeine intake should be restricted to less caffeine than used in the present study, such as one to two cups of coffee per day (100-150 mg of caffeine).

This study does not support the relationship between the arrhythmia severity or inducibility and elevations in plasma epinephrine levels and hypokalemia. The elevation in norepinephrine levels following caffeine approached statistical significance ($p=0.053$). This elevation may be important as a mechanism of arrhythmia induction since epinephrine infusions have previously been shown to induce sustained ventricular arrhythmias in normal patients. It is unknown if norepinephrine levels are elevated with electrophysiology testing alone .

Clinical Significance

The popularity of coffee has made consumption of this beverage a common practice by many people, including cardiac patients. The conclusions gained from this study will add to the current scientific knowledge regarding coffee. This information will allow health practitioners to counsel cardiac patients about

the safety of coffee ingestion. This knowledge can be applied to various inpatient and outpatient settings such as coronary care units and cardiac rehabilitation programs. Advice from this study should be restricted to those patients who have a history of ventricular tachycardia or ventricular fibrillation and coronary artery disease. This advice can be shared with patients from all age groups and with any concurrent cardiac medications.

When counseling patients about their limitation in caffeine intake, an individual caffeine consumption history must first be obtained. As previously discussed, the amount of caffeine per serving of coffee and tea varies due to preparation method, brewing time and raw material used (refer to pages 3-6). Robusta coffee beans (seldom used due to poor taste) contain a higher percent of caffeine than arabica beans (found in gourmet coffee shops). Canned coffee found in grocery stores contain a combination of these beans. After assessing the patients' method of practice for preparing coffee or tea, an approximation of his/her daily caffeine intake can be calculated. A plan should be outlined for the patient, using his/her individual consumption history and practice methods, that will restrict caffeine intake to 100-150 mg/day (refer to Appendix G for caffeine content).

Instructions must be given about other beverages (beside coffee and tea), food items, and medications that contain caffeine. Concern must also be given with regard to coffee consumption and other methylxanthines such as theophylline products. The combination of the two items may further increase the risk for arrhythmias in cardiac patients.

Limitations

The patients evaluated in this study consisted of those with a history of cardiac disease and prior ventricular arrhythmias. The results from this study

can be generalized to only those patients with a history of similar cardiac disease since caffeine administration has resulted in a different responses between normal subjects and those following acute myocardial infarction (as shown by other researchers).

Study Design

The study could be strengthened by using a double-blind control design. A randomization of the caffeine-free and caffeine electrophysiology test, with a serving of decaffeinated coffee, might have eliminated subject or researcher bias. It is possible that a serving of coffee may have made the subject more relaxed, and produced a lowered epinephrine response, since coffee drinking is an addiction for some people. The researcher's interaction with the subject after caffeine may have also influenced the results in a positive or negative manner.

The current design used for this study was most reasonable for the clinical situation in which these patients were involved. This study occurred while elective electrophysiology evaluation was taking place. It was not possible to change the current electrophysiology schedule for these patients. Also, it was not possible to expose some patients to the research treatment while not exposing others, because of ethical reasons and increased risk due to electrophysiology testing.

Sample selection by nonprobability may have limited the selection of female subjects, patients with cardiomyopathy, and younger age subjects. The group is not a homogeneous sample. Subject selection from a heterogeneous population has increased the risk of bias.

This study is also limited by its small sample size. A larger sample would have been more representative of the population, and thus the sampling error would have been smaller.

Lack of control of individual circadian aspects may have weakened this study. Measurements of ventricular arrhythmias, catecholamines, and potassium concentration may have been more consistent if they were measured at equal circadian times for each subject.

Laboratory Measurements

A larger sample group would have reduced the variance in catecholamine measurements. Improvement in catecholamine laboratory techniques would have achieved increased accuracy.

Caffeine administration

All subjects did not attain similar blood levels of caffeine. This is due to the variation in individual half lives. Therefore, electrophysiology, catecholamine and potassium results are not subjected to a uniform variable (caffeine). To avoid the variability in caffeine concentrations, individual plasma caffeine peak times and half-lives would have had to be determined prior to beginning the study. Unfortunately, this would have increased the subject's time involvement and prolonged their hospital stay.

The serving of coffee was determined by three laboratory measurements from a standard recipe. Every coffee sample was not individually measured for caffeine concentration. Therefore, the variation in the amount of caffeine consumed between subjects is unknown .

Future Research

Future research would be aimed towards a continuation of this research project with a double-blind control design and increased sample size. The

patient sample would only include patients with ventricular arrhythmias secondary to CAD, because there is a larger population of this patient type undergoing electrophysiology testing. This would also narrow the subject sample to one type of patient group. Improvements would be made towards catecholamine laboratory measurements.

Other research questions have become apparent from this study. It would be interesting to compare caffeine and coffee in relation to plasma potassium concentrations. Since coffee contains a small amount of potassium, it is hypothesized that an equal serving of caffeine and coffee (in terms of milligrams) will affect plasma potassium levels differently. Plasma potassium might decrease one hour after caffeine tablets and not after a serving of coffee. Other caffeine beverages (tea, soda pop) could be substituted for caffeine tablets to determine if the lack of plasma potassium changes are unique to coffee alone.

It would be intriguing to determine if a relationship exist between theophylline products, coffee and increased severity of arrhythmias. Coffee would be given to patients already on therapeutic doses of theophylline and electrophysiology testing would follow.

Measurement of arrhythmias after acute or chronic coffee ingestion would be useful information. This evaluation could take place during acute ingestion (one electrophysiology testing period) or chronic coffee ingestion (several electrophysiology testing periods or long-term Holter monitoring). This would further increase the understanding of short term and long term coffee ingestion in patients with ventricular arrhythmias.

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Appendix A

Scoring Classification

Scoring Classification

Severity Score	Arrhythmia induced
1	No induced arrhythmia or atrial arrhythmias
2	1-3 repetitive ventricular response (RVR)
3	4-6 beats of non-sustained ventricular tachycardia (NSVT)
4	≥ 7 beats of NSVT, lasting less than 30 seconds
5	Ventricular tachycardia (VT) at rate 100 to 160 beats per minute (bpm)
6	VT at rate 161 to 200 bpm
7	VT at rate 201 to 300 bpm
8	VT at rate > 300 bpm or ventricular fibrillation

The severity of the arrhythmia increases as the score increases (Kudenchuk et al., 1986).

Inducibility Score	Type of Stimuli
1	Four extrastimuli (E4), or no ventricular arrhythmia induced with any type of stimuli
2	Three extrastimuli (E3)
3	Two extrastimuli (E2)
4	One extrastimulus (E1)

The ease of inducing ventricular arrhythmias increases as the score increases.

Appendix B

Research Check-List

Research Check-List

Subject's Name_____

Inclusion/Exclusion Criteria Check-List:

- ____ Age between 35 to 80.
- ____ History of coffee consumption prior to origination of ventricular arrhythmias.
- ____ Cardiac origin of ventricular arrhythmias.
- ____ Hemodynamic stability: blood pressure, heart rate.
- ____ Serum electrolyte values within normal range.
  - potassium 3.5-4.7 mEq/L (mmol/L)
  - sodium 136-147 mEq/L (mmol/L)
  - chloride 98-109 mEq/L (mmol/L)
  - calcium 8.5-10.5 mg/dL (mmol/L)
- ____ Absence of pregnancy or lactation.
- ____ Absence of renal or hepatic failure.
- ____ No documented psychological disorder.
- ____ No use of oral contraceptives, cimetidine, theophyllne related drugs, quinolone antibiotics (Norfloxacin, Nalidixic acid, Prefloxacin, Ofloxacin, Ciprofloxacin, Amifloxacin Enoxacin).
- ____ No sustained ventricular tachycardia or ventricular fibrillation requiring cardioversion (to end the arrhythmia) during the initial or caffeine-free electrophysiology test.
  - ____ 1st baseline:
  - ____ 2nd baseline:

Protocol check list:

- ____ Indwelling catheter in place; central or peripheral (blood can be drawn from this line).
- ____ All antiarrhythmic drugs (including beta blockers) stopped 24-36 hours prior to first baseline electrophysiology test (except calcium channel blockers and digoxin).
- ____ No caffeine consumption 24 hours prior to second baseline electrophysiology test.

Appendix C

Consent Form

Oregon Health Sciences University
INFORMED CONSENT FORM

Title

Caffeine and Arrhythmias: An Electrophysiologic Approach

Purpose

I understand that I am being invited to participate in an experimental research study by Linda Burd Chelsky, RN, graduate nursing student and Dr. John McAnulty, Professor of Cardiology. The purpose of this study is to learn if coffee ingestion is safe for people who have a history of ventricular arrhythmias (fast heart rate).

Goals

1. To determine if coffee ingestion increases the possibility of arrhythmias (fast heart rate) or makes the arrhythmias worse (faster heart rate or longer duration of the fast heart rate).

2. To examine the relationship between changes in catecholamine (or adrenaline, a substance normally produced in the body during times of stress) blood levels and arrhythmias after drinking 250 mg of caffeine (the amount of caffeine found in two strong cups of coffee).

3. To examine the relationship between changes in potassium blood levels and arrhythmias after drinking 250 mg of caffeine (the amount of caffeine found in two strong cups of coffee).

Procedures

I have previously agreed to have my heart arrhythmias evaluated by electrophysiology testing. I understand that if I participate in this coffee research study, I will undergo an additional electrophysiology test. This additional test will be called the "caffeine electrophysiology test". It will take place after my first two baseline electrophysiology tests (electrophysiology test without drugs).

The "second baseline test" and the "caffeine test" will take place while I am in the Coronary Care Unit. Twenty-four hours before the "second baseline test" I will not be allowed to drink or eat caffeine (coffee, tea, coke, pepsi, hot chocolate, chocolate cake or ice cream, coffee flavored desserts, others). Directly after the "second baseline test" I will be expected to drink two cups of coffee that contain a total of 250 mg of caffeine (two servings of coffee that are stronger than normal) within 15 minutes on an empty stomach. The "caffeine electrophysiology test" will take place 45 minutes after drinking the two cups of coffee, and the test will last less than 30 minutes (similar to the "second baseline test").

I will be interviewed for 10-15 minutes within two days after the "caffeine electrophysiology test". I will be asked about my previous caffeine intake, my cigarette smoking status and my sleeping patterns. My medical records will be reviewed by the researchers for information about my medical history, my medications, and my age before the "second baseline test".

Blood Test

I understand approximately 12 ml of blood (two teaspoon) will be drawn from an indwelling catheter (a small plastic tube in a vein that is already in place) prior to my "second baseline test" and 15 ml of blood (one tablespoon) will be drawn prior to my "caffeine electrophysiology test". The blood draw will not be painful because the blood comes from an indwelling catheter. The blood will be used for measurement of potassium and catecholamine blood levels before and after coffee ingestion. A caffeine blood level will be measured after drinking coffee.

Thus, I realize that the only additional testing procedures which I am being asked to participate in beyond routine electrophysiologic testing are:

1) No intake of coffee or caffeine products 24 hours prior to the "second baseline test".

2) Drinking two cups of strong coffee 60 minutes prior to the "caffeine test".

3) Blood specimens prior to the "second baseline test" and "caffeine test".

4) The "caffeine electrophysiology test".

Risk

I understand that by participating in this caffeine study there is a possibility that I may experience heart arrhythmias one more additional time. My "caffeine electrophysiology test" will take place with trained cardiologists (heart doctors) and nursing staff under the supervision of Dr. McAnulty or one of his colleagues. If I do have sustained ventricular arrhythmias (a fast heart rate that does not stop unless treatment is used) after drinking coffee, I will be treated with medicine, burst pacing (several fast heart beats given by a pacemaker using the wire that is already in place in my heart through my shoulder), or electrical shock with the paddles. If my ventricular arrhythmia does not respond to the listed treatment, it is possible that I could die. The possibility of this occurring is rare. As of this date, no one has had arrhythmias associated with electrophysiology testing that could not be treated (at the Oregon Health Sciences University hospital). If my arrhythmias need to be stopped with the paddles, it is possible that I could throw up (coffee). The chance of this occurring is very small.

Discomforts

I may experience discomfort with drinking a strong cup of coffee on an empty stomach. I may have some stomach upset; I may feel restless and shaky; I may feel flutters in my chest, or I may need to urinate. I may also experience caffeine withdrawal symptoms such as headache, irritability, drowsiness, and decreased alertness. This "caffeine electrophysiology test" should not prolong my hospital stay.

Benefits

By participating in this research study, I will gain personal benefits by knowing how my ventricular arrhythmias respond to coffee and/or caffeine products. Medical science will benefit by my participation, since it may help health care practitioners to understand whether coffee does or does not contribute to ventricular arrhythmias.

Confidentiality

I understand that as a subject in this research study, all information about me will be kept strictly confidential. My name or my personal identity will not be used for public purpose, publication or transmitted outside the Oregon Health Sciences University.

Compensation

"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."

I understand there will be no personal cost involved in this caffeine study and I will not be paid to participate.

I have talked with Linda Burd Chelsky, RN and/or Dr. John McAnulty, and they have offered to answer any questions I have. If I have further questions, I may reach Linda Burd Chelsky at 293-0339 or Dr. McAnulty at 279-8581.

I understand that I may refuse to participate or withdraw from this study at any time without affecting my relationship with or treatment at the Oregon Health Sciences University.

Oregon Health Sciences University
INFORMED CONSENT FORM
Caffeine and Arrhythmias: An Electrophysiologic Approach

I have read the foregoing and agree to participate in this study.

Subject's signature	Date
Witness	Date

Appendix D

Coffee Recipe

Coffee Recipe

36 gm of Yuban Coffee

700 cc of water at 190 degrees Celsius

1). Place coffee in french press coffee maker.

2). Add hot water.

3). Place lid on french press with filter above water. Steep 5 minutes.

4). Push filter through coffee mixture.

5). Serve 500 cc of prepared coffee to the patient.

The patient may have 30 cc of milk and/or 1 teaspoon of sugar to go with the 500 cc serving of coffee.

Appendix E

Chart Review

Chart Review

Subject identification number _____

Date of caffeine electrophysiology test _____

1. Age _____
2. Gender _____
3. What is the subject's baseline rhythm? _____
4. Describe the subject's ventricular arrhythmias.

   _____

   type of EKG documentation _____

   symptoms during arrhythmias (syncope, chest pain)

   _____

   _____
5. How long has the patient been know to have ventricular arrhythmias?

   _____
6. When was the last episode of spontaneous ventricular arrhythmias? _____

   _____
7. Does the subject have a history of atrial arrhythmias?

   _____ Yes

   _____ No

8. List medical history.

_____

_____

_____

_____

_____

_____

_____

9. List current medications, dose and frequency.

_____

_____

_____

_____

_____

_____

10. List date and value of most current serum electrolyte levels.

	Date	Value
potassium	_____	_____
sodium	_____	_____
chloride	_____	_____
calcium	_____	_____

11. Height _____

Weight _____

Appendix F

Interview Questions

Interview Questions

Subject identification number _____

1. How many servings of the following beverages did you drink per day prior to your first experience of heart arrhythmias (fast heart beat)?

   decaffeinated coffee

   _____ instant

   _____ percolated

   _____ brewed

   _____ other, please specify _____

   caffeinated coffee

   _____ instant

   _____ percolated

   _____ brewed

   _____ other, please specify _____

2. How many servings of the following beverages did you drink after your first experience of heart arrhythmias (fast heart beat)?

   decaffeinated coffee

   _____ instant

   _____ percolated

   _____ brewed

   _____ other, please specify _____

caffeinated coffee

_____ instant

_____ percolated

_____ brewed

_____ other, please specify _____

3. Do you ever feel palpatations (flutters) in your chest or dizziness after drinking caffeinated coffee?

_____ yes

_____ no

4. How many of the following caffeinated beverages do you normally drink a day? Please state the size of serving (8 ounce or one cup, 12 ounce, 16 ounce, etc.).

Number of servings		Size of serving
_____	Pepsi-cola	_____
_____	Mr. Pibb	_____
_____	Jolt	_____
_____	Hot cocoa	_____
_____	RC cola	_____
_____	Coke/coca-cola	_____
_____	Mountain dew	_____
_____	Mellow yellow	_____
_____	Big red	_____
_____	Kick	_____
_____	Hot/ice tea	_____
_____	Ice tea (instant)	_____
_____	Ice tea (can)	_____

Number of servings		Size of serving
_____	Tab	_____
_____	Chocolate milk	_____
_____	Dr. Pepper	_____
_____	Diet rite	_____
_____	Cherry cola	_____
_____	Aspen	_____
_____	Candian dry Jamica cola	_____

5. Do you ever feel palpitations (flutters) in your chest or dizziness after drinking the above beverages?

_____ yes

_____ no

6. Do you take any of these medication on a daily basis? If so, how many tablets do you take per day.

Medication	Yes	How many ?
A.P.C.	____	_____
Aspirin compound	____	_____
Amaphen	____	_____
Anacin	____	_____
Anoquan	____	_____
Appedrine	____	_____
Aqua-Ban	____	_____
Broma-seltzer	____	_____
Bromoquinine	____	_____
Buff-A Comp	____	_____
Cafamine	____	_____

Medication	Yes	How many?
Cafergot	____	_____
Codexin	____	_____
Cope	____	_____
Coryban-D	____	_____
Compal	____	_____
Darvon	____	_____
Dex-A-Diet II	____	_____
Dexatrim	____	_____
Di-Gesic	____	_____
Dristan	____	_____
Duradyne-Forte	____	_____
Easy-mens	____	_____
Efed II	____	_____
Empirin	____	_____
Esgic	____	_____
Excedrin	____	_____
Fiorinal	____	_____
G-1 capsules	____	_____
Korigesic	____	_____
Medigesic plus	____	_____
Midol	____	_____
Migral	____	_____
No Doz	____	_____
Pacaps	____	_____
Permathene H2 Off	____	_____

Medication	Yes	How many?
Pre-mens	____	_____
Prolamine	____	_____
Repan	____	_____
Sinarest	____	_____
SK-65 Compound	____	_____
Soma	____	_____
Synalgos-DC	____	_____
T-Gesic	____	_____
Triaminicin	____	_____
Two-dyne	____	_____
Vanquish	____	_____
Vivran	____	_____
Wigraine	____	_____

7. How much chocolate do you normally eat a day?

   _____ small amounts

   _____ moderate amounts

   _____ large amounts

8. Do you smoke cigarettes?

   _____ no

   _____ yes

   How many packs a day ? _____

   How many years have you smoked cigarettes? _____

9. What time do you normally go to sleep? _____

10. What time do you normally wake up? _____

Appendix G
Caffeine Content of Beverages, Food Items and Medications

Caffeine Content of Beverages, Food Items and Medications

Item	Milligrams
Beverages	
Coffee (6 oz.)	
Brewed (drip)	138
Percolator	96
Instant	78
Decaffeinated	3
Tea (6 oz.)	
Brewed	60
Instant	36
Iced (12 oz.)	70
Hot Chocolate (6oz.)	5
Chocolate milk (8oz.)	5
Soda Pop (12 oz.)	
Coca-cola, Coke, Cherry Cola	46
Tab	47
Mr. Pibb	41
Dr. Pepper	40
Pepsi-cola	38
RC Cola	36
Diet Rite	36
Jolt	71

Mountain Dew	54
Mellow Yellow	53
Big Red	38
Kick	31
Aspen	36
Candian Dry Jamica Cola	30
Others Soda Pop (12oz.)	
Sugar-Free Mr. Pibb	59
Shasta Cola, cherry cola, diet cola	44
Sugar-Free Dr. Pepper	40
Sugar-Free Big Red	38
Diet Pepsi, Pepsi Light	36
Sunkist Orange	0

Food Items	Milligrams
Baking chocolate	35/oz.
Bitter Sweet chocolate	30/oz.
Baker's chocolate	26/oz.
Dark chocolate, semi-sweet	20/oz.
Milk chocolate	6/oz.
Chocolate-flavored syrup	4/oz.

Medications	Milligrams
Analgesics	
A.P.C.	32/tablet
Amaphen	40/tablet
Anacin, Anacin Maximum Strength	32/tablet

Anoquan	40/capsule
Buff-A Comp	40/tablet
Cafergot, Cafergot P.B.	100/tablet or suppository
Darvon Compound, Darvon Compound 65	32.4/tablet
Dia-gesic	30/tablet
Empirin	0/tablet
Esgic	40/capsule
Excedrin Extra Strength	65/tablet
Fiorinal, Fiorinal with Codeine	40/tablet or capsule
G-1 capsules	40/tablet
Korigesic	30/tablet
Medigesic plus	40/capsule
Midol, Midol Maximum Strength	0/caplet
Migralam	100/capsule
Pacaps	40/capsule
Repan	40/tablet
SK-65 Compound	32.4/tablet
Soma Compound, or with Codeine	0/tablet
Synalgos, Synalgos-DC	30/capsule
Two-dyne	40/tablet
Vanquish	33/caplet
Wigraine	100/tablet
Weight Control Agents	
Appedrine	100/tablet
Codexin	200/tablet
Dex-A-Diet II	200/tablet

Dexatrim	0/tablet
Prolamine	140/tablet
Duretics	
Aqua-Ban	100/tablet
Permathene H2 Off	200/tablet
Pre-mens Forte	100/tablet
Cold and Allergy	
Coryban-D	30/tablet
Dristan	0/tablet or capsule
Duradyne-Forte	30/tablet
Sinarest, extra Strenght, No Drowisiness	0/tablet
Triaminicin	0/tablet
Stimulant	
Efed II Black	200/capsule
No Doz	100/tablet
Vivran	200/tablet

("Caffeine: How to", 1981; Lecos, 1984; Raebel & Black,1984; Physicians' Desk Reference, 1986; Physicians' Desk Reference, 1987; Physicians' Desk Reference, 1988; PDR for Nonprescription Drugs, 1988; Physicians' Desk Reference,1989).

Appendix H

Results

Electrophysiology Results

Subject identification number _____

Electrophysiology Test	Date	Time	Results*
Initial test	_____	_____	_____
Caffeine-free test	_____	_____	_____
Caffeine test	_____	_____	_____

* See Rhythm Score (see appendix A)

Laboratory Results

Test	Date	Time	Results
Caffeine-Free Test			
Epinephrine	_____	_____	_____
Norepinephrine	_____	_____	_____
Potassium	_____	_____	_____
Caffeine Test			
Epinephrine	_____	_____	_____
Norepinephrine	_____	_____	_____
Potassium	_____	_____	_____
Caffeine	_____	_____	_____

Appendix I

Revision of Severity Scoring Method

Revision of Severity Scoring Method

Severity Score	Arrhythmia Induced
1	0-3 beats of repetitive ventricular response(RVR).
2	4 beats to less than 30 seconds of non-sustained ventricular tachycardia (NSVT).
3	Ventricular tachycardia (VT) at rate 100-200 beats per minute (bpm).
4	VT at rate 201-300 bpm.
5	VT at rate >300 bpm or ventricular fibrillation.

The severity of the ventricular arrhythmia increases as the score increases.

Abstract

Title: The Effect of Coffee on Ventricular Arrhythmias in Cardiac Patients.

Author: Linda Burd Chelsky

Approved: [redacted]

Advisor

This quasi-experimental study was implemented to determine if caffeine ingestion, in the form of coffee, was safe for patients who have a history of ventricular tachycardia or ventricular fibrillation. Changes in plasma catecholamine and potassium levels were also evaluated in relation to rhythm severity and inducibility. Coffee ingestion with this type of patient sample has not been previously investigated. Subjects were selected by nonprobability sampling. Twenty-two patients, 86% with coronary artery disease, who were undergoing electrophysiology evaluation in an inpatient setting were given coffee with 275 mg of caffeine. An electrophysiology test was performed before and 45 minutes after coffee ingestion and blood samples were obtained prior to each test.

The mean plasma caffeine level was 6.2 ± 0.5 mg/L (SEM). The mean plasma epinephrine ($p=0.46$), norepinephrine ($p=0.053$), and potassium ($p=0.18$) levels did not change significantly (t-test analysis) after coffee. Induced rhythms were unchanged in 17 (77%), more severe in 2 (9%) and less severe in 3 (14%) patients. The number of extrastimuli required to induce a rhythm after coffee was unchanged in 10 (46%), decreased in 6 (27%), and increased in 6 (27%) patients.

In these patients with documented ventricular tachycardia or fibrillation, coffee did not alter the severity or inducibility of ventricular arrhythmias ($p>0.05$, Wilcoxon summed rank analysis). There were no significant correlations between changes in plasma concentrations and increased severity or ease in

inducibility of ventricular arrhythmias ($p>0.05$, Spearman's rank order correlation). Despite the lack of significant changes in ventricular arrhythmias after coffee with 275 mg of caffeine, some patients did demonstrate an increase in rhythm severity and inducibility. Therefore, coffee or caffeine ingestion in this patient sample should be restricted.