DIGITALIS IN BI- AND TRIFASCICULAR DISEASE: ITS EFFECT ON HIS-PURKINJE CONDUCTION TIME IN MAN

By

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s.m.k.

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CHAPTER I

Introduction

Conceptually, the His-Purkinje system in man consists of the His bundle and the three fascicles (1,2) connecting the atrioventricular (AV) node to the ventricles: the right bundle branch, the anterior fascicle of the left bundle branch, and the posterior fascicle of the left bundle branch. These pathways allow the transmission of an electrical impulse from the atria to the ventricles. Patients with bifascicular disease have disease in two of the three conduction pathways. Patients with trifascicular disease have disease in all three fascicles of the His-Purkinje system.

Significant disease of the His-Purkinje conduction system often slows or completly blocks the velocity of the electrical impulse in one, two, or all three specialized conduction pathways. This conduction slowing or block can be documented, in man, by two methods. First, patterns of block in the bundle branches can be recognized on the surface electrocardiogram (3). Second, an intracardiac electrocardiogram, known as a His bundle electrocardiogram, provides a method for recording and measuring His-Purkinje conduction time (4-9). The clinical measure of His-Purkinje conduction time obtained from the His bundle electrocardiogram is called the HV interval (7). If the HV interval is prolonged, the patient is diagnosed as having trifascicular disease (5). The correlation between a prlonged HV time and trifascicular disease has been confirmed by pathologic study (10). Since patients with bi- or trifascicular disease already exhibit some degree of conduction slowing in two or all three pathways of the ventricular specialized conduction system, they may be more likely to advance to complete heart block than patients with normal intraventricular conduction (11-20). Digitalis therapy has also been

shown to precipitate complete heart block in some patients (21). Therefore, it is important to know if digitalis therapy adds to the risk of developing complete heart block in patients with bi- or trifascicular disease.

The term digitalis is used generally to refer to any of the cardioactive steroids or steroid glycosides which exert inotropic and electrophysiologic effects on the heart. These effects are explained in terms of molecular structure. All cardioactive glycosides exhibit an unsaturated lactone ring, a C-14 hydroxyl group, and a *cis* fusion of the C and D rings of the steroid nuclues (2,22). The seven most commonly used glycosides are derived from three different plants. Digitoxin, gitalin, and digitalis leaf come from the leaf of the *Digitalis purpurea*. Digoxin, lanatoside C, and deslanoside are obtained from *Digitalis lanata*. Ouabain, a fast-acting cardiac glycoside, is an exception and is not derived from the *Digitalis* genus. Ouabain, extracted from the seed of the *Strophanthus gratus*, is the digitalis preparation employed in this study.

Clinically, digitalis is often the treatment of choice for: 1) ventricular dysfunction with resultant congestive heart failure; or 2) for certain recurrent supraventricular tachyarrhythmias. About 80 per cent of the patients with His-Purkinje disease, as evidenced by bi- or trifascicular block, have associated heart disease (23) and often develop heart failure or tachyarrhythmias for which digitalis therapy may be the prescribed treatment. Therefore, the effects of this drug on patients with an already compromised conduction system should be explored.

Before examining the electrophysiologic effects of digitalis on automaticity, excitability, refractoriness, or conduction in compromised cardiac conduction tissues, the normal patterns of cardiac impulse formation and conduction, at the cellular level, are reviewed.

Review of the Literature

The Action Potential

In the normal, resting cardiac cell, the potential difference across the cell membrane can be measured at -80 to -90 millivolts (mv) (24). The interior of the cell is negative with respect to the exterior. Whenever a stimulus to the cell is strong enough to decrease the magnitude of the resting potential to -55 or -60 mv, the threshold potential is reached. At threshold levels, a self-propagating action potential begins. This action potential represents a rapid depolarization and reversal of membrane potential followed by repolarization and gradual return to the resting level. Any subthreshold stimulus is not able to elicit a self-sustaining depolarization as described above.

The action potential consists of four phases. The first phase, phase 0, starts with rapid depolarization and ends when a potential difference of approximately +25 mv is recorded across the cell membrane, the interior of the cell is now positive with respect to the exterior. Phase 1 is characterized by fast repolarization, bringing the potential difference to 0 mv. Then a slowing of repolarization occurs and phase 2, the plateau phase, results. Phase 3, also repolarization, is more rapid and brings the potential back to the resting level. The return to resting transmembrane potential is called phase 4 (24).

With the onset of phase 0, the refractory period of the action potential begins. During the refractory period, the cell is not excitable by a threshold stimulus. Initially, the cell is absolutely refractory. During the absolute refractory period, no impulse can be generated. In time, however, as the membrane repolarizes to approximately -55 mv, submaximal responses can be evoked by stimuli exceeding the resting threshold level. The end of the effective refractory period is marked by the

earliest propagated response. Then, as membrane potential continues to repolarize toward -90 mv, the supernormal period occurs. During this period, the stimulus needed to excite the cell is less than the stimulus needed to excite a fully recovered cell. However, the evoked response is submaximal. Finally, resting potential is again achieved. The normal transmembrane action potential and responses to a series of stimuli are shown in figure 1.

Just the tissues of the sinoatrial(SA) node, atrium, atrioventricular (AV) node, His-Purkinje fibers, and ventricles are different, the configuration of the action potential, which represents the change in voltage as a function of time, is slightly different for each of the specific tissue types. However, all four phases are present in every case (24). By algebraically summing the action potentials from many cardiac cells, a clinical counterpart of the action potential can be recorded as the surface electrocardiogram. The electrocardiogram allows observation of the voltage time course for the electrical events of the entire cardiac cycle (2-4). The QRS complex is coincident with phase 0, the ST segment represents phase 2, and phase 3 corresponds to the T wave. The diagrammatic representation of the transmembrane action potential and a unipolar electrogram are shown in figure 2.

Basically only two cell types exist in the heart, muscle and conduction cells. The major electrical difference between the two cell types is seen in phase 4 of the action potential. Conduction cells, i.e., cells of the SA node, AV node, and ventricular specialized conduction system (His-Purkinje system), are capable of spontaneous phase 4 depolarization to threshold potential, a phenomena known as diastolic depolarization. In other words, these cells are capable of intrinsically generating and sustaining action potentials during phase 4. Diastolic

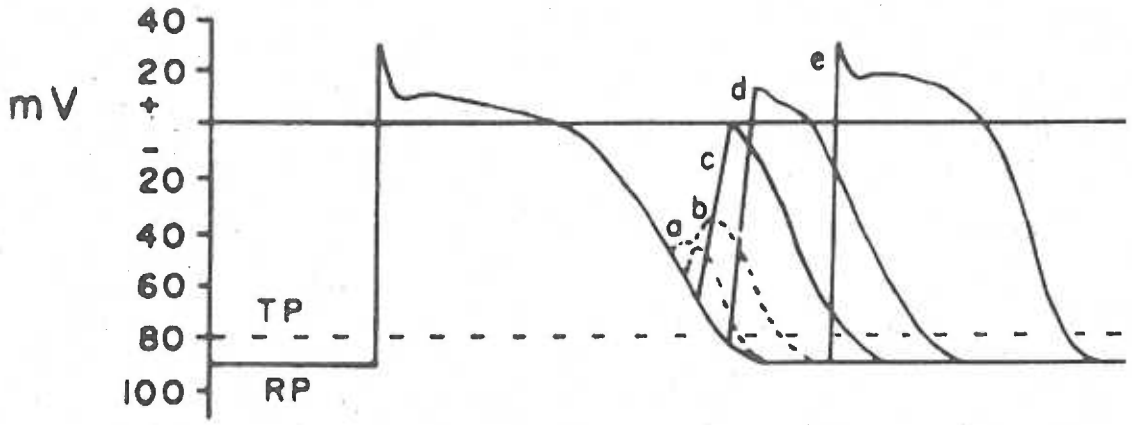

Figure 1. Normal transmembrane action potential and responses to a series of stimuli, Responses (a and b) do not propagate. Prior to submaximal response (a) the preparation was totally refractory. Response (c) the earliest propagated response marks the end of the effective refractory period. Response (d) occurs during the supernormal period. Response (e) is a normally propagated response occurring when repolarization is complete -- from Hoffman and Singer (24).

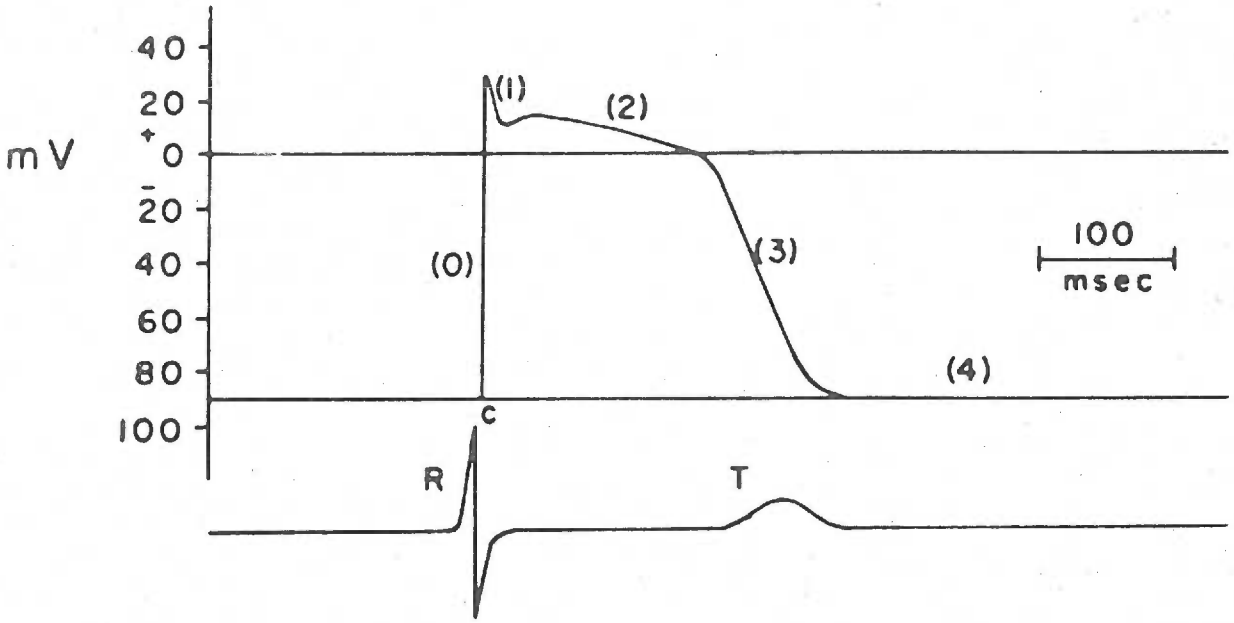

Figure 2. Diagrammatic representation of transmembrane action potential and unipolar electrogram recorded from isolated preparation of cardiac muscle. At (c), action potential is initiated. Phases 0, 1, 2, 3, and 4 of the action potential are shown. The bottom trace shows the intrinsic deflection of the R wave of the electrogram to coincide with 0 of the action potential. The T wave is synchronous with phase 3 -- Hoffman and Singer (24).

depolarization accounts for automaticity, or the ability of certain cardiac cells to initiate and propagate an impulse. In fact, automaticity of pacemaker cells determines the rate and rhythmicity of the heart. Automatic activity at the cellular level increases when the slope of phase 4 depolarization increases and the magnitude of the resting potential becomes more negative or when the threshold potential lowers (24, 25).

Excitability and conduction velocity are also affected by action potential characteristics. Both excitability and conduction velocity increase with increased slope of phase 0, increased amplitude of the action potential and enhanced negativity of the resting potential (24,25).

Biochemical Basis for the Action Potential

The time course of excitability, automaticity, conduction and refractoriness of single cell, monophasic action potentials has a biochemical basis. The electrical potential difference across the cell membrane is a function of the diffusion potential created from the separation of charged ions by the semipermeable cell membrane. At resting potential, the membrane is more permeable to the potassium ion (K^+) than to the sodium ion (Na^+). Therefore, as quantitated by the Nernst and Goldman equations (26), the resting membrane potential represents the diffusion potential of K^+. The concentration of K^+ is greater intracellularly than extracellularly. The reverse is true for the concentration of Na^+ (26,27). This concentration gradient, at resting potential, is maintained by an active transport process called the Na^+K^+ pump. In this process, K^+ is actively transported intracellularly and Na^+ is actively transported extracellularly in order to maintain the concentration gradient. The energy for transport is provided by hydrolysis of adenosine triphosphate,

a process regulated by membrane adenosine triphosphatase. This enzyme is stimulated by K+ extracellularly and Na+ intracellularly, thus providing homeostatic control mechanism at the cellular level (24-28).

When cells depolarize and propagate an action potential, the potential difference across the cell membrane grows more positive. This increasing positivity reflects changes in cell membrane permeability to K+ and Na+, as well as changes in the concentration gradients of these ions. At phase 0, the cell membrane becomes more permeable to Na+ than to K+. Sodium conductance increases. As Na+ diffuses into the cell, the interior becomes positive with respect to the exterior. As repolarization progresses, Na+ permeability decreases, and K+ permeability increases. While K+ diffuses extracellularly, the membrane potential is restored to its former resting level. At the end of repolarization, Na+ has accumulated intracellularly, and K+ has accumulated extracellularly. Then the Na+K+ pump transports Na+ outward and K+ inward. Since the membrane is now more permeable to K+, the K+ gradient again dominates the transmembrane potential at -80 to -90 mv, the resting level (21,24-29).

The Ionic Basis for Digitalis Effects

The action of digitalis glycosides on myocardial transmembrane potentials reflects the effects of digitalis on membrane permeability and the ionic flux of Na+ and K+. Langer suggests that digitalis inhibits the membrane Na+K+ adenosine triphosphatose activity, not competitively, but by binding to an allosteric site on the enzyme (28). Thus, extracellular K+ concentration increases while intracellular Na+ concentration increases. This study indicates that Na+ efflux from the cell is not linked to K+ influx via the Na+K+ pump alone. When the pump is inhibited by digitalis, an exchange of Na+ for calcium ions (Ca++) occurs thereby augmenting the free Ca available intracellularly. Free intracellular Ca

has been linked to the inotropic response (28). The discussion of inotropy is not included in this report.

The action of digitalis on the His-Purkinje fiber system has been studied, in vitro, using microelectrode techniques, (24,27,28). At lower concentrations of this glycoside, changes occur initially in the repolarizing phases of the action potential, phases 2 and 3. The duration of phase 2 decreases while phase 3 increases, producing no change in the total action potential duration (24,27). These changes probably result from increased K+ permeability due to inhibition of the Na+K+ pump by digitalis (24,26,27). This increased K+ permeability causes a decreased membrane resistance. Since, at this point, no change in resting potential has occurred, a stronger stimulus is required for excitation. This phenomeno can be explained by Ohm's law, voltage = current x resistance. Therefore, excitability decreases (24,27-29).

Ionic Basis for Digitalis Toxicity

Toxic doses of digitalis cause repolarization to accelerate and the action potential duration to decrease, thus shortening the effective refractory period. Further depletion of intracellular K+ stores resulting from Na+K+ pump inhibition causes a decrease in the magnitude of the resting potential and the cells become more easily excitable. Concurrently, a decrease in the rate of rise of phase 0 and a decrease in the amplitude of the action potential result, thus slowing conduction velocity. This decrease in the rate of rise of phase 0 is caused by impaired Na+ conductance at the time of depolarization. In other words, when the resting potential decreases in magnitude, Na+ conductance decreases and the Na+ current necessary for depolarization cannot be generated (24,27-29).

At the same time, changes are also apparent in phase 4 depolarization.

Either the slope of phase 4 diastolic depolarization increases and causes ectopy, or generation of low amplitude potentials occurs (30). When the slope of phase 4 progressively increases, automaticity increases as well. If, on the other hand, low amplitude potentials result, then phase shifts can occur. Phase shifts occur whenever low amplitude potentials alter the resting membrane potential. Successive action potentials then originate at different levels of membrane potential (21,24,30). Since excitability and conduction depend on the level of resting potential at the time of stimulation, low amplitude potentials could either enhance or hinder excitability at any given time.

In summary, for His-Purkinje cells, as alternations in K+ permeability accelerate repolarization, the effective refractory period shortens, the magnitude of the resting potential decreases, and the slope of phase 4 diastolic depolarization increases, possibly generating low amplitude potentials. These changes allow, initially, for enhanced excitability and automaticity seen clinically as ectopy. With further loss of resting potential due to decreased intracellular K+ concentration and decreased Na+ conductance, the cells become inexcitable and block results. In digitalis toxicity, with the appearance of ectopy and block, the framework for reentrant arrhythmias is established (31,32).

Effect of Digitalis on the Intact Heart

The effect of digitalis on the excitability, refractoriness, and conduction of the SA node, atrium, and AV node has also been studied in the laboratory in the intact heart (33-40). The digitalis effect has been attributed to either:

1) indirect or autonomically mediated actions,
2) direct action on conduction tissue and heart muscle, or
3) a combination of 1 and 2 above.

For example, slowing the rate of impulse formation in the SA node by decreasing the rate of phase 4 depolarization may be a combined direct and indirect (antiadrenergic) effect of a low dose of digitalis. Paradoxically, higher doses of the drug cause increased rate of impulse formation in atrial pace maker cells (33-35). In the atrial muscle, depression of resting excitability and slowing of intra-atrial conduction velocity are due to a direct effect of digitalis alone (36-40). Though, at first, the vagally mediated (indirect) action of digitalis may shorten the atrial effective refractory period, eventually, the direct effect of the glycoside causes lengthening of the effective refractory period. It is interesting to note that in the intact preparation, the combined direct and indirect effects cause lengthening of the effective refractory period (34,35). Digitalis slows conduction through the AV node both by vagal stimulation and by a direct effect. The effective refractory period of the AV node is prolonged by both vagal and direct effects as well (33-40), even though the action potential duration shortens. This increased effective refractory period may represent decremental conduction in the node (31).

Digitalis Effects on the Conduction System of Man

Whether digitalis affects intra-atrial conduction in man remains controversial. Engel and Schaal (41) demonstrated no significant change in intra-atrial conduction time following administration of intravenous ouabain to 9 patients with sick sinus syndrome. On the other hand, Dhingra, Amat-Y-Leon, Wyndham, Wu, Denes, and Rosen (40) showed significant prolongation of the intra-atrial conduction time and the atrial effective refractory period in 16 patients receiving ouabain. Researchers agree, however, that digitalis does increase block in the AV node (41,42).

Since digitalis can increase block (decremental or otherwise) in AV nodal conduction tissue, then digitalis might be expected to affect the His-Purkinje conduction tissue in a similar fashion.

Statement of the Problem

Patients with disease of the His-Purkinje tissue, i.e., bi- or trifascicular disease, are presumed to be at higher risk of developing complete heart block (11-20), than patients with normal intraventricular conduction. Digitalis therapy has also been shown to precipitate complete heart block in some patients. Approximately 80 per cent of patients with bi- or trifascicular disease have associated heart disease (23) and often require digitalis therapy. Although digitalis does not prolong His-Purkinje conduction time (quantitated by the HV interval) in patients without conduction defects (43), the drug could increase the HV time in patients with evidence of compromised ventricular conduction, i.e., bi- or trifascicular disease. If the drug prolongs His-Purkinje conduction time in patients with bi- or trifascicular disease, then it should be used with caution in that patient group.

Purpose of the Study

The purpose of this study is twofold:

1) To document any systematic or significant variation in the HV interval over time in patients with bi- or trifascicular disease.
2) To document the effect of ouabain on conduction through the His-Purkinje tissue in patients with bi- or trifascicular disease.

Definitions

For the purposes of this study standard electrocardiographic definitions were used (44):

1. Right bundle branch block (RBBB)
   a. QRS duration = 0.12 seconds or greater
   b. The presence of notched R wave, RR', RSR', (or QR if previous infarction is present) in lead V_1
   c. ST depression and T wave inversion in lead V_1
2. Left bundle branch block (LBBB)
   a. QRS duration = 0.12 seconds or greater
   b. The presence of broad, monophasic notched R wave in V_6
   c. ST depression and T wave inversion in lead V_6
   d. Absence of both S wave and Q wave in V_6
   e. Atypical LBBB is diagnosed if there is an S wave or a Q wave in V_6
3. Left axis deviation (LAD):
   Mean frontal QRS axis more negative than -30^{o}
4. Right axis deviation (RAD):
   Mean frontal QRS axis more positive than $+90^{o}$
5. First degree atrio-ventricular (AV) block:
   PR interval greater than 0.20 seconds.

The standard electrophysiologic intervals were measures in milliseconds (msec) from the His bundle electrocardiogram which is described in methodology. The intervals were defined as follows:

1. PA - the interval from the onset of the P wave of the ECG to the first rapid atrial deflection on the His bundle electrocardiogram (8) representing intra-atrial conduction time

2. AH - the interval from the first rapid atrial deflection on the His bundle electrocardiogram to the first high frequency component of the His spike (8), representing AV nodal conduction time
3. HV - the interval between the first high frequency component of the His spike to the earliest initial deflection of the QRS on the surface ECG (7), representing His-Purkinje conduction time
4. Sinus node recovery time (SNRT) - the interval between the last paced P wave to the first spontaneous sinus P wave following cessation of pacing. Pacing was done for 1 minute at rates 110, 120, and 130 prior to abrupt cessation and measurement of SNRT (9).

The upper limit for the normal HV interval was defined as 55 msec (6). The relationship of the surface ECG to the His bundle electrocardiogram is shown in figure 3.

Bi- and trifascicular disease were defined as follows:

1. Bifascicular disease:
   a. Right bundle branch block (RBBB) plus left axis deviation (LAD)
   b. RBBB plus right axis deviation (RAD)
   c. Left bundle brnach block (LBBB)

   Any of the above three states could be accompanied by PR prolongation. Patients with PR prolongation could have trifascicular cisease. Proof of trifascicular disease must be obtained on His bundle electrocardiography by a prolonged HV interval. Patients with bifascicular disease have a

normal HV interval ($\leq$ 55 msec) (6).

2. Trifascicular disease:

   a. RBBB plus alternating LAD and RAD

   b. RBB alternating with LBBB

   c. Bifascicular block plus prolonged HV interval (HV $>$ 55 msec) (6).

CHAPTER II

Methodology

Patient Selection

The 48 patients in this study group were drawn from the patient population at the University of Oregon Health Sciences Center Hospital and Clinics and the Portland Veteran's Administration Hospital and Clinics, from 1974 through 1976. During this time period, the University of Oregon Health Sciences Center maintained a 465 bed hospital with a daily census of 412, and averaged 4600 outpatient visits per month. The Portland Veteran's Administration Hospital had 523 beds, with an average daily census of 469, and saw 5,003 patients per month on an outpatient basis. Patients utilizing these two facilities resided in Oregon, Idaho, Washington, Northern California.

Daily ECG review at both hospitals identified potential patients for inclusion in the study. The University of Oregon Health Science Center averaged 1200 ECG's per month while the Portland Veteran's Administration provided 1167 tracings per month for review. Identified inpatients were contacted in person and asked whether they chose to participate in this research study during the current hospitalization. Outpatients were requested to attend a cardiac conduction clinic. The clinic invitation appears in Appendix A. At the time of the clinic visit, the outpatients were also asked whether they chose to participate in this research study. Final patient selection was based on surface ECG patterns and willingness to participate in the research protocol. Written informed consent was obtained from all subjects. The consent form appears in Appendix B. Patients on prescribed digitalis were requested to withhold the glycoside for two weeks prior to His bundle electrocardiography.

Electrophysiologic Studies

His bundle studies were performed (4-9) on all patients by the usual method. A tripolar catheter was inserted percutaneously through the right femoral vein and, under fluoroscopy, positioned across the tricuspid valve into the right ventricle. The catheter was withdrawn slowly across the valve until a rapid biphasic or triphasic deflection appeared between the atrial and ventricular electrograms and within the PR interval of the surface ECG. Recordings were made on a multichanel oscilloscopic photographic recorder (Electronics for Medicine DR-16) at paper speeds of 100 and 200 mm/second. His bundle activity was recorded at filter frequently settings of 40 to 500 HZ. Multiple ECG leads were recorded simultaneously, usually leads I, II, III and V_1. A quadripolar catheter was passed from an antecubital vein into the high right atrium. Two electrodes sensed the high right atrial depolarization which was also recorded. The remaining two electrodes served to pace the atrium. Patients were paced at increasing rates starting at 10 beats/minute higher than the intrinsic sinus rate and advancing at 10 beats/minute increments until Wenckebach periods, advanced AV block, or symptoms such as angina were observed, or until a heart rate of 160 to 200 beats/minute occurred. Control conduction intervals and intervals with atrial pacing were recorded.

The effect of ouabain on conduction in the His-Purkinje tissue was assessed by noting a change in the HV interval 45 minutes after ouabain administration.

Ouabain is the most polar and rapidly acting cardiac glycoside used clinically (22). The onset of action is within 5 to 10 minutes of infusion and the peak effect occurs within 30 to 120 minutes. The average

half-life of ouabain is 21 hours. This drug follows first order kinetics and is metabolized mainly through the kidneys with minimal gastrointestinal excretion. Ouabain is available for intravenous use only. The average digitalizing dose is 0.3 to 0.5 mg (22). The dose of ouabain used in this study was 0.015 mg/kg.

Patient Groups

The 48 patients were divided into four study groups at time of His bundle electrocardiography (HBE):

Group A: Eight patients with bi- or trifascicular disease not receiving ouabain

Group B: Ten patients with normal intraventricular conduction receiving ouabain

Group C: Seventeen patients with bifascicular disease receiving ouabain

Group D: Thirteen patients with trifascicular disease receiving ouabain

After measurement of control conduction intervals, Groups B, C, and D were given intravenous ouabain, 0.015 mg/kg over 15 minutes. Forty-five minutes later the electrophysiologic studies were repeated because the maximum physiologic affect of the glycoside had been demonstrated to occur at that time (45). Although Group A did not receive ouabain, the initial measurements were repeated at the end of one hour in order to determine the natural variation in conduction intervals.

Included in this study were 33 men and 15 women whose mean age was 67.2 ± 1.9 ($\pm$ standard error of the mean)with a range of 35 to 95 years. Thirty-eight patients evidenced bi- or trifascicular disease on surface ECG or on His bundle electrocardiography. Ten patients had normal intraventricular conduction patterns on ECG and normal conduction intervals on

His bundle electrocardiography. Age and sex distribution, surface ECG pattern, and associated cardiovascular disease for the different groups appear in Appendix C.

Statistical Methods

Within groups, the student's paired t-test was used to determine any significant mean HV interval difference in pre-versus 45 minutes post-ouabain measurements. The unpaired t-test was performed between the bifascicular disease patients (Group C) and the trifascicular disease patients (Group D) to detect any between group difference in the percent change of the HV interval pre-versus post-ouabain infusion. The students paired t-test was performed on Group A in order to quanitate the possible significant spontaneous variation of HV interval with time. Any p value of greater than 0.05 was considered to be non-significant.

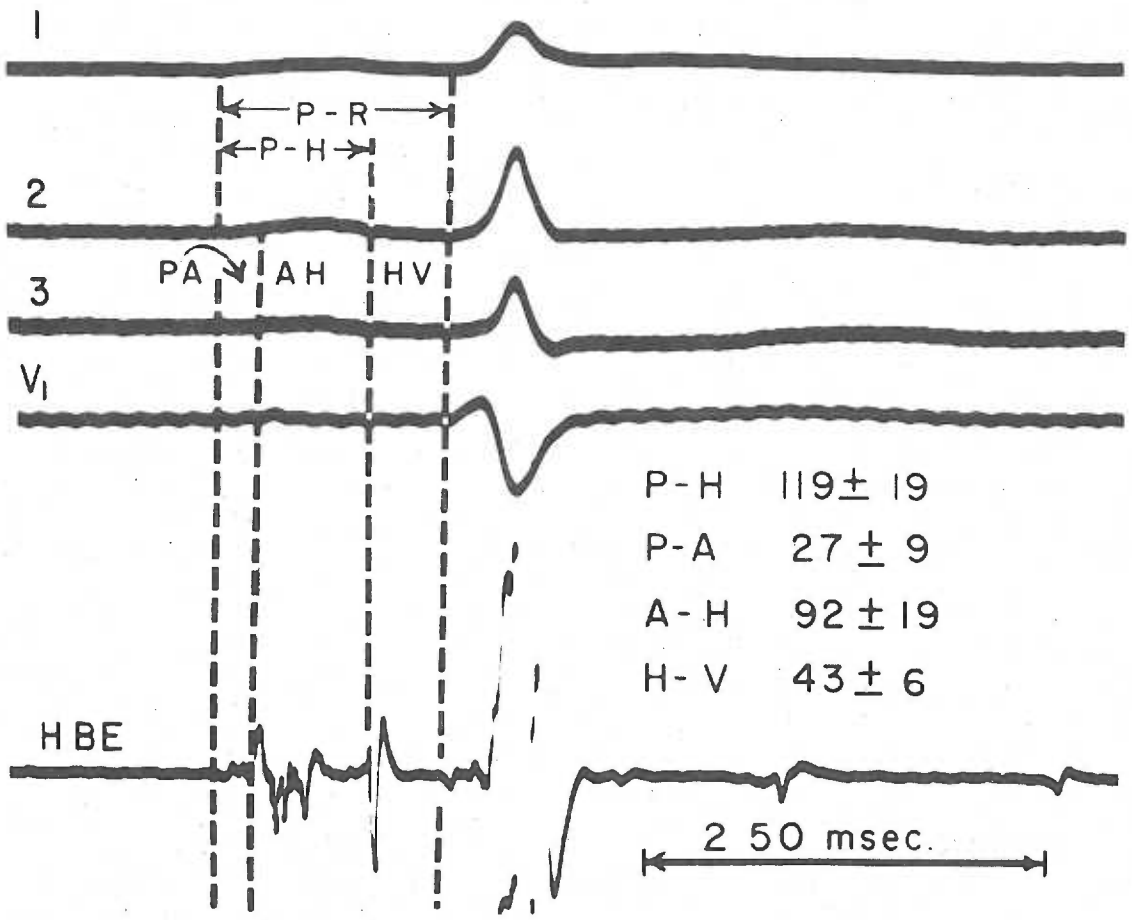

Figure 3. Measurement of conduction intervals. Shown are ECG leads 1, 2, 3, and V_1, as well as the His bundle electrocardiograms (HBE). Paper speed is 200 mm/sec. Mean ± the standard deviation of normal conduction intervals is shown.--- from Dhingra, Rosen, and Rahimtoola (6).

CHAPTER III

Results

Electrophysiologic intervals were measured in all 48 patients initially and at the end of 1 hour for Group A; or 45 minutes after administration of intravenous ouabain for Groups B, C, and D. Intervals measured included heart rate (HR), PA interval, AH interval, HV interval, sinus node recovery time (SNRT), and heart rate at the time of appearance of the Wenckebach phenomenon. These electrophysiologic variables are listed by group in Appendix D for all individuals. Differences in before and after measurements were tested within groups at the .05 significance level by the students' paired t-test. Differences between Groups C and D were analyzed by the unpaired t-test at the .05 level of significance. All values are reported as the mean $\pm$ the standard error of the mean (SEM).

Group A

In Group A, the 8 patients with intraventricular conduction defects not receiving ouabain, the control HV interval (mean $\pm$ SEM in msec) was 67 ± 2.7 changing to 64 ± 2.4 after one hour. The HV interval varied with time by 7 ± 1.5 percent, however, this spontaneous variation was not statistically significant ($p \geq .05$). HV time increased in two cases and decreased in six. The absolute value of the mean interval change was 4.75 ± 1.07. Figure 4 shows the initial and one hour HV measurements for Group A. Heart rate, PA interval, and AH interval also did not change ($p > .05$) with time. T-tests were not performed on the sinus node recovery time and heart rate at the development of Wenckbach periods because missing values decreased the sample size precluding meaningful statistical analysis. Mean intervals and levels of significance for the spontaneous variation of conduction intervals appear in Table 1.

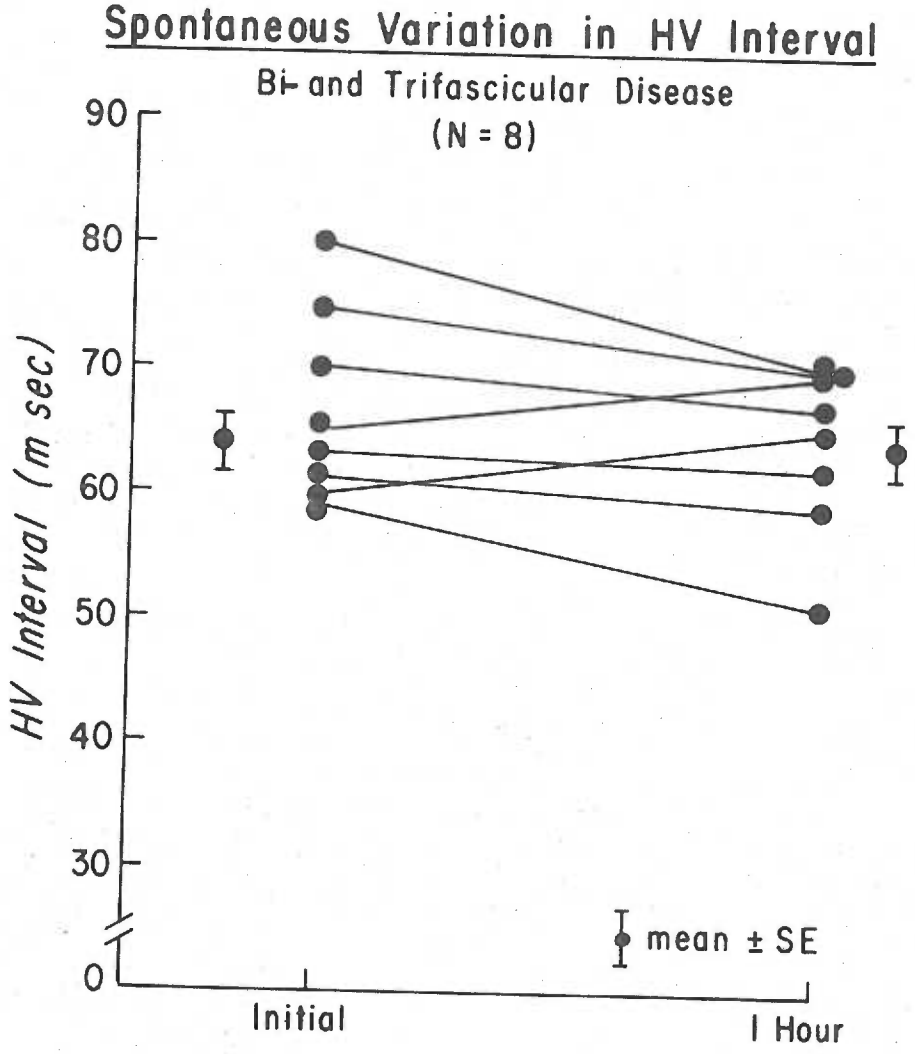

Figure 4. Initial and 1 hour HV measurements for the 8 patients in Group A. Mean ± the standard error (SE) are shown.

TABLE 1

Results of Paired T-Test and Statistical Levels of Significance for Initial and One Hour Measurement Of Conduction Intervals in Group A

Measurements	Initial	1 Hour	p value
HR (beats/min)	71 ± 4.5	71 ± 3.9	> .05
PA (msec)	48 ± 8.6	58 ± 7.0	> .05
AH (msec)	82 ± 9.6	74 ± 10.2	> .05
HV (msec)	67 ± 2.7	64 ± 2.4	> .05
SNRT (msec) at rate 130	-- ---	-- ---	--
HR at Wenckebach (beats/min)	-- ---	-- ---	--

all values mean ± SEM

Group B

Ouabain did not alter HV conduction in Group B, the 10 patients with normal intraventricular conduction. Analyzed by the students' paired T-test, HV intervals pre-ouabain (49 ± 3.4) were not significantly different from post-ouabain (47 ± 2.9) values ($p > .05$). HV time increased in one case, decreased in 7, and remained the same in two. The control HV measurements and the measurements 45 minutes after ouabain are shown in figure 5. The absolute value of the mean interval change was 2.1 ± .53 representing a 4.4 ± 1.1 percent variation. The sinus node recovery time and heart rate at the time of appearance of the Wenckebach phenomenon were not analyzed because missing values decreased the sample size, precluding meaningful statistical information. The heart rate, PA interval, and AH interval showed no significant change pre - versus 45 minutes post-ouabain as analyzed by the students' paired T-test. The electrophysiologic interval means pre- and post-ouabain and the level of statistical significance appear in Table 2.

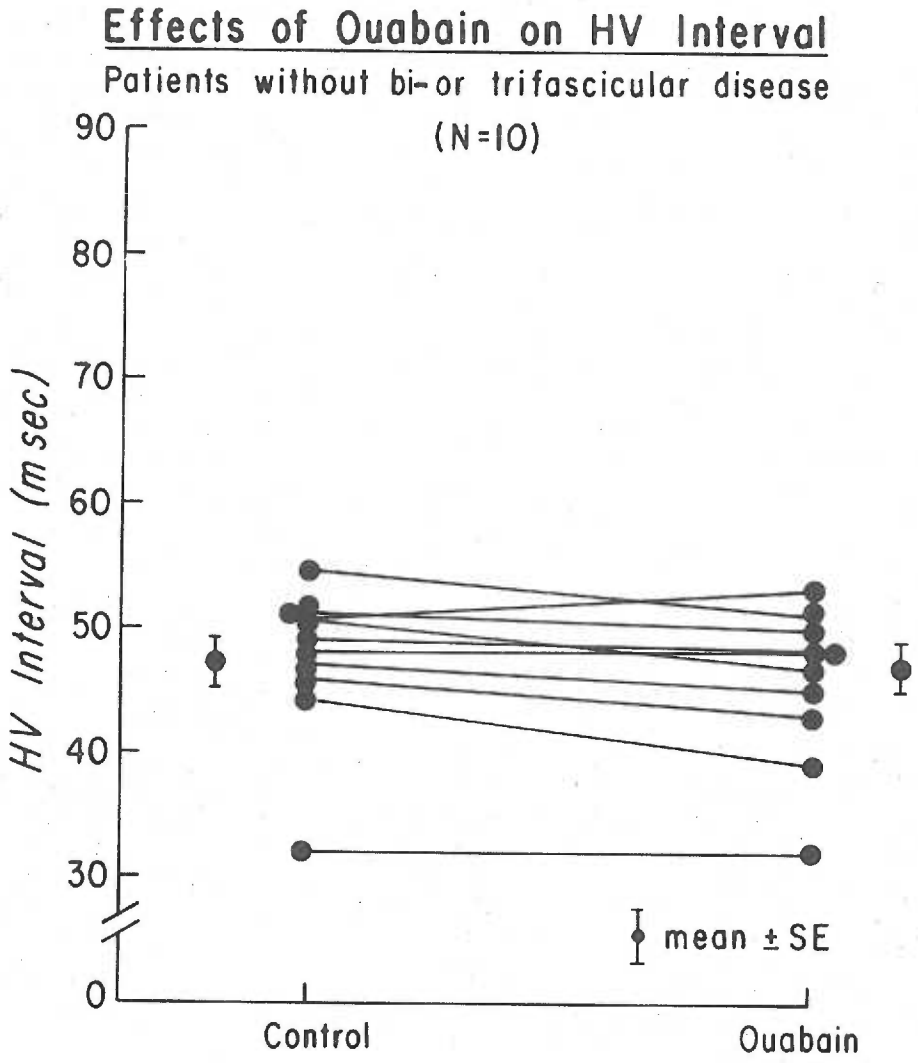

Figure 5. Control and 45 minutes after ouabain HV measurements for the 10 patients in Group B. Means ± standard error (SE) are shown.

TABLE 2

Results of Paired T-Test and Statistical Levels of Significance for the Measurement of Control and 45 Minutes after Ouabain Conduction Intervals in Group B

Measurements	Control	45 Minutes Later	p value
HR (beats/min)	68 ± 5.3	71 ± 7.9	> .05
PA (msec)	34 ± 6.1	32 ± 6.3	> .05
AH (msec)	105 ± 13.5	158 ± 36.7	> .05
HV (msec)	49 ± 3.4	47 ± 2.9	> .05
SNRT (msec at rate 130	---	---	
HR at Wenckebach (beats/min)	---	---	

all values mean ± SEM

Groups C and D

The mean HV interval for Group C, the 17 patients with bifascicular disease, was 46 ± 1.3 which changed to 47.0 ± 1.6 after ouabain ($p > .05$). The absolute value of the mean change was 3.4 ± .79 representing a variation of 6.5 ± 1.5 percent. The HV interval decreased in 7 cases (4.7 ± 1.3), increased in 9 (2.8 ± .74) and remained the same in one. The HV intervals pre- and post- ouabain for Group C appear in figure 6. The heart rate, PA interval, AH interval, sinus node recovery time, and heart rate at the time of appearance of the Wenckebach phenomenon were not significantly different as analyzed by the paired t-test.

For the 13 subjects with trifascicular disease, the mean HV interval was 66 ± 2.8 changing to 66 ± 2.2 ($p > .05$) after ouabain. HV time decreased in 7 cases (3.4 ± .6) and increased in 6 (3.2 ± 1.0). Figure 7 shows HV interval changes after ouabain for the patients in Group C. The absolute value of the mean HV change was 3.3 ± .6 representing a 5 ± 1.0 percent variation. The heart rate, PA interval, sinus node

recovery time, and heart rate at the time of appearance of the Wenckebach phenomenon were not significantly different pre-versus 45 minutes post-ouabain, as analyzed by the paired t-test. However, the AH interval did prolong from the control value of 106 $\pm$ 7.2 to 123 $\pm$ 8.4 45 minutes after ouabain ($p < .01$).

The mean HV variation (3.3 $\pm$ 0.6) for Group D was not significantly different from the mean HV variation (3.41 $\pm$ .07) for Group C when analyzed by the unpaired t-test ($p > .05$) between groups.

Groups C and D were combined for further analysis. The HV interval pre-ouabain (55 $\pm$ 2.2) was not significantly different from the post-ouabain value (55 $\pm$ 2.3) in the 30 patients with bi- or trifascicular disease ($p > .05$). The absolute value of the mean HV interval change was 3.4 $\pm$ 0.5 representing 6.4 $\pm$ .98 percent variation. HV time increased in 15 cases (2.93 $\pm$ .57), decreased in 14 (4.07 $\pm$ .75), and remained the same in one. Control and 45 minutes after ouabain HV measurements for the 30 patients in Groups C and D appear in figure 8. The heart rate, PA interval, sinus node recovery time, and heart rate at the time of appearance of the Wenckebach phenomenon were not different pre-versus 45 minutes post-ouabain. However, the AH interval for the patients with bi- or trifascicular disease change significantly from the control value of 99 $\pm$ 4.7 to 111 $\pm$ 6.5 after ouabain ($p < .01$). The electrophysiologic interval means pre- and post- ouabain and the level of statistical significance appear in Table 3.

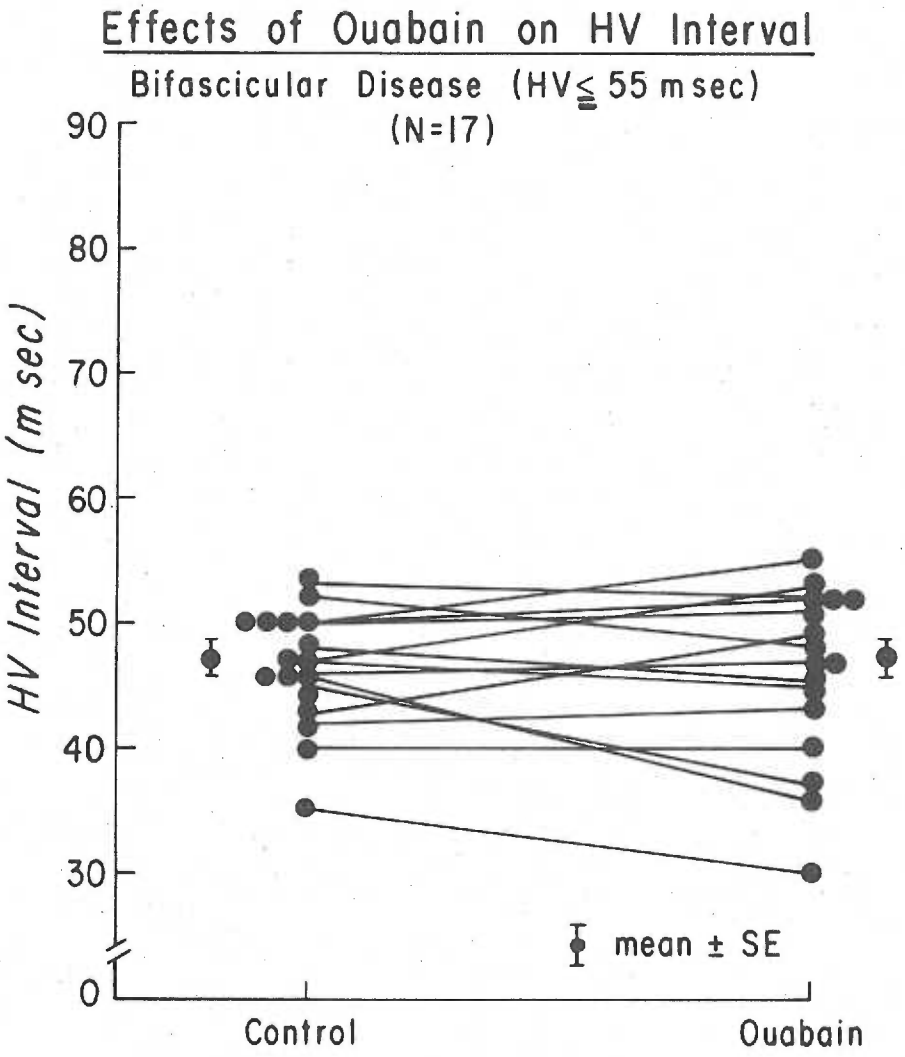

Figure 6. Control and 45 minutes after ouabain HV measurements for the 17 patients with bifascicular disease. Means ± SE (standard error) are shown.

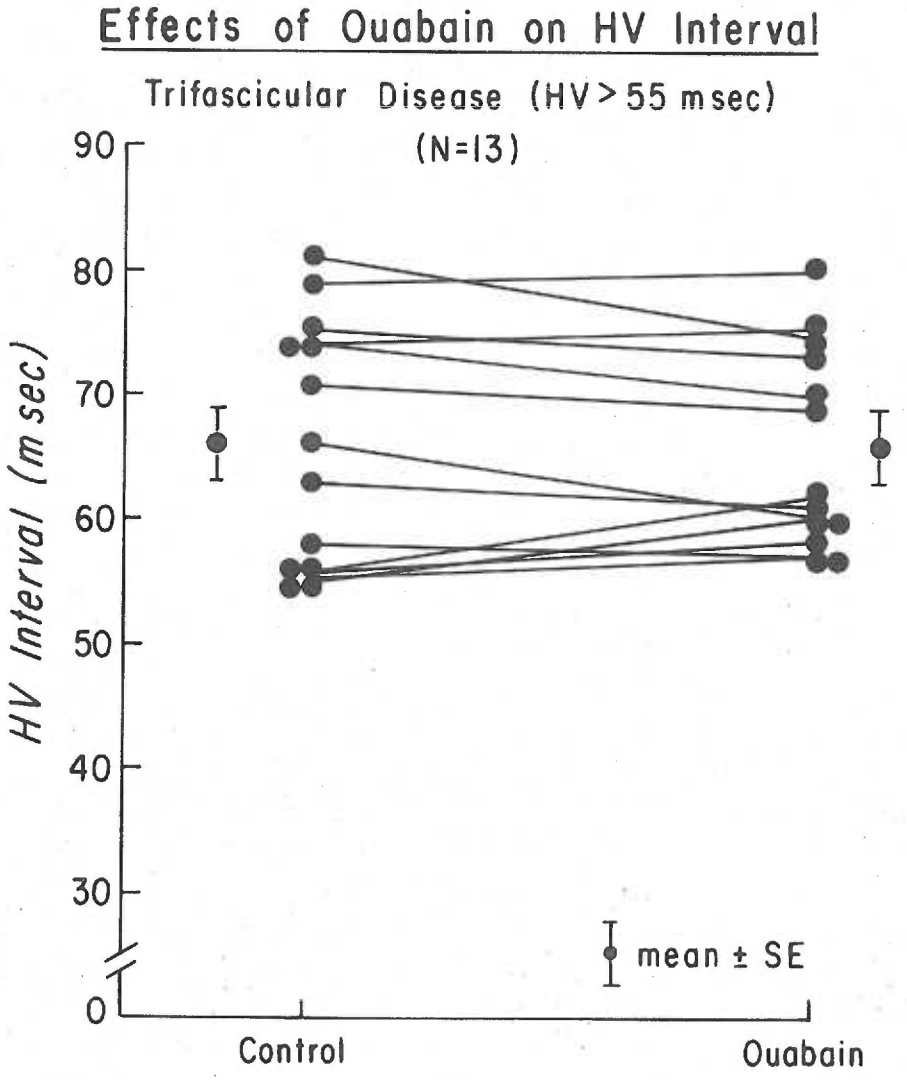

Figure 7. Control and 45 minutes after ouabain HV measurements for the 13 patients with trifascicular disease. Means ± SE (standard error) are shown.

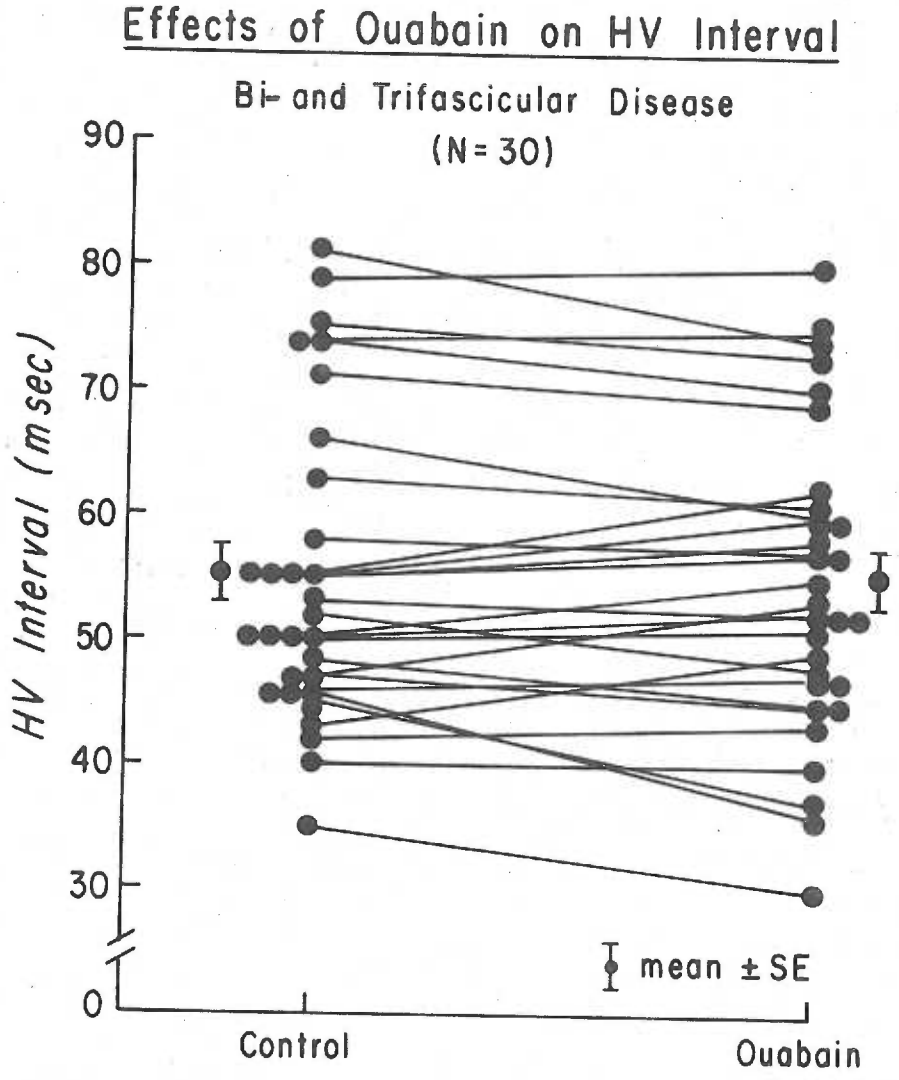

Figure 8. Control and 45 minutes after ouabain HV measurements for the 30 patients with bi- or trifascicular disease. Means ± SE (standard error) are shown.

TABLE 3

Results of Paired T-Test and Statistical Levels of Significance for Measurement of Control and 45 Minutes after Ouabain Conduction Intervals in Groups C and D

Measurements	Control	45 Minutes Later	p value
HR (beats/min)	73 ± 2.6	72 ± 2.8	> .05
PA (msec)	41 ± 4.0	45 ± 3.8	> .05
AH (msec)	99 ± 4.7	111 ± 6.5	< .01
HV (msec)	55 ± 2.2	55 ± 2.3	> .05
SNRT (msec) at rate 130	1006 ± 30.7	1019 ± 76.9	> .05
HR at Wenckebach (beats/min)	133 ± 9.2	126 ± 6.5	> .05

all values mean ± SEM

Although ouabain increased the resting HV interval in 15 of 30 (50%) patients with bi- or trifascicular disease, it also decreased resting HV time in 14. No significant change in HV interval was documented in patients with bi- or trifascicular disease receiving intravenous ouabain.

CHAPTER IV

Discussion

The effects of digitalis, at therapeutic and toxic doses, on the voltage time course of monophasic action potentials of the His-Purkinje system have been studied in the laboratory (24, 27, 30, 33-39). Both in vitro and intact animal models have shown digitalis to initially increase ectopy and excitability. With further exposure to the glycoside, decreased excitability, slowed conduction, and block result.

Smith and Haber (21) have reviewed the evidence that digitalis induces disturbances of cardiac impulse formation, automaticity, and refractoriness in man. They report that, at toxic levels, glycosides often precipitate complete heart block (21). Several investigators believe that the presence of bi- or trifascicular conduction disease also imposes an increased risk of complete heart block (11-20).

Approximately 80 percent of the patients with bi- or trifascicular disease have associated heart disease (23) and often require digitalis therapy for resultant congestive heart failure and/or certain recurrent arrhythmias. At therapeutic levels, digitalis does not prolong His-Purkinje conduction time in patients without conduction defects. However, assuming that His-Purkinje disease can be a precursor of complete heart block, digitalis treatment, even at therapeutic levels, might be expected to increase the chance of advanced block in already compromised conduction tissue.

In man, the clinical measure of His-Purkinje conduction is the HV interval. An excellent correlation exists between prolonged HV time and the presence of tribascicular disease at time of autopsy (10). However, Rosen (46) did report one exception. In this case, a patient with

left bundle branch block and a normal HV time exhibited significant disease of the left bundle branch and the right bundle branch on anatomic section. The HV time was normal, but the patient had documented trifascicular disease.

Pathologic studies have shown a positive correlation between increased HV time, i.e., trifascicular disease, and the appearance of complete heart block (47). Vera, Mason, Fletcher, Awan, and Massumi (20) claim that patients with trifascicular disease and bundle branch block on ECG for at least three years are a high risk subgroup for the development of complete heart block. A markedly prolonged HV time has also been shown to be prognostically significant, especially for those patients with recent myocardial infarction (48). Other authors question the precision of the HV interval as a predictive tool (49). These authors believe that HV time has limited value in describing progression to complete heart block, or in predicting which subgroup of bi- or trifascicular disease patients will advance to complete heart block.

The reliability and replicability of the HV interval from one time of measurement to the next has not previously been examined. The present study attempted to document the natural variation of the HV interval in a group of 8 patients with bi- or trifascicular disease. By measuring a control HV interval, waiting one hour, and again recording the HV time, a 7 ± 1.5 percent variation of the HV interval with time was demonstrated. This variation was neither systematic nor statistically significant. The 95 percent confidence interval for this normal percent variation was 4.2 percent to 9.8 percent.

Patients with normal intraventricular conduction are reported to experience no HV prolongation with digitalis therapy (43). The present study also determined that the 10 patients with normal intraventricular

conduction, who received intravenous ouabain, showed no significant change in HV interval. However, the effects of ouabain on patients with compromised intraventricular conduction had not previously been reported. Therefore, this investigator also examined the effects of digitalis on patients with bi- or trifascicular disease. The HV interval was used as the specific marker for changes in His-Purkinje conduction. No significant or systematic HV variation was demonstrated. In the 30 patients with bi- or trifascicular disease, HV time increased in 15 cases, decreased in 14, and remained the same in one. The absolute value of the mean change was $3.4 \pm .79$ msec representing a 6.5 ± 1.5 percent variation. This variation was not statistically significant and possibly represents the normal variation described above.

It was noted that one individual with bifascicular disease increased HV time by 6 msec or 13 percent after ouabain, while the HV time in a patient with trifascicular disease decreased by 10 msec post-ouabain, a change of 21 percent. A change of 13 percent and 21 percent respectively, may be significant for the individual patient since these percent changes do not fall within the 95 percent confidence interval for random spontaneous variation of HV interval measurement, shown to range from 4.2 to 9.8 percent. Examples such as these two indicate the need for caution in applying group statistics to individual cases. In addition, the fact that 15 of 30 (50%) patients with bi- or trifascicular disease experienced an increase in resting HV time after ouabain necessitates consideration of other methods of evaluation of His-Purkinje conduction. Possibly other methods such as measurement of refractory periods (50-52) and His bundle pacing (53-54) could define a smaller effect of digitalis on His-Purkinje tissue.

Digitalis can affect conduction velocity and/or refractoriness. Conduction system disease can produce abnormalities of conduction velocity and/or refractoriness as well. The HV time reflects the conduction velocity in the His-Purkinje system and coincides with depolarization (phase 0) of the action potential. Refractory periods, on the other hand, relate to total action potential duration (phases 0, 1, 2, and 3). If refractory periods as well as conduction intervals were analyzed in patients with bi- or trifascicular disease receiving ouabain, perhaps a digitalis effect could be detected.

Since the beginning of this study, routine measurement of the refractory periods of the atrium and AV node, by extra stimulus technique, (50-52) has begun. The relative refractory period of the His-Purkinje system is obtained when possible, and, perhaps, the effective refractory period of the bundle branches can also be obtained. Unfortunately, in anywhere from 25 to 75 percent of cases, block occurs in the atrium or AV node before the His-Purkinje system becomes refractory (50-52). This response is termed a type A response (52,55).

In order to obtain refractory information in cases of type A response, His bundle pacing has been utilized (53-54). By pacing at the level of the His bundle, problems with intra-atrial or AV nodal block occurring before His-Purkinje block, can be circumvented. His bundle pacing, when successful, stresses the ventricular specialized conduction system to the point of refractoriness and block. While some investigators claim to be routinely successful at His bundle pacing (53,54), others succeed at pacing the His bundle in only 15 to 20 percent of type A cases (56). If this success rate improves, His bundle pacing will prove valuable in defining subgroups of patients at greater risk of developing block in the His-Purkinje system with digitalis therapy, possible patients with bi- or trifascicular disease.

In this study, 15 of 30 (50 percent) of the patients with bi- or trifascicular disease demonstrated an increased HV time after ouabain. This increase was not statistically significant. However, if His bundle pacing were employed in this patient group, in order to fully stress the His-Purkinje system, a significant change in refractory periods after ouabain infusion might be demonstrated, and a high risk subgroup defined. By pacing the His bundle and measuring the effective refractory period of the bundle branches, pre- and post- ouabain changes in His-Purkinje conduction might be better delineated.

CHAPTER V

Summary and Conclusions

Laboratory studies on His-Purkinje tissue in animal models have shown that predictable changes occur in the voltage and the time course of the action potential as the concentration of the glycoside increases. Initially, the effective refractory period shortens, the magnitude of the resting potential decreases, and the slope of phase 4 increases thereby increasing automaticity and excitability. With further loss of resting potential and a decrease in the amplitude and rate of rise of phase 0, conduction velocity slows and block occurs. It would seem that parallel changes should be observable clinically, especially in a group of patients already exhibiting block in two or all three fascicles of the ventricular conduction system.

To date, the clinical measure of His-Purkinje conduction time is the HV interval. Digitalis does not prolong His-Purkinje time in patients without conduction defects. However, the effect of ouabain on the HV interval in patients with bi- or trifascicular disease has not previously been reported. Also, whether the HV interval is intrinsically reliable and replicable from the time of one measurement to the next has never been examined.

The purposes of this study were to:

1) document any systematic or significant variation in the HV interval over time in patients with bi- or trifascicular disease.
2) document the effect of ouabain on conduction through the His-Purkinje tissue in patients with bi- or trifascicular disease.

The results of this study showed that the HV interval varied, during the electrophysiologic procedure, by 7 $\pm$ 1.5 percent in 8 patients with bi- or trifascicular disease. However, this spontaneous variation was neither systematic nor statistically significant. No significant difference in HV conduction time was demonstrated 45 minutes after intravenous ouabain was administered to 30 patients with bi- or trifascicular disease.

Therefore, the following conclusions were drawn:

1) although a 7 percent variation in the HV interval did occur with time, this variation was neither systematic no significant. The value of the HV interval was not affected by the time of measurement during the electrophysiologic study.
2) the HV time did not prolong following the administration of intravenous ouabain to patients with bi- or trifascicular disease.

Assuming the HV time to be a precise and reliable measure of His-Purkinje conduction, patients with bi- or trifascicular disease do not appear to be at increased risk of developing advanced block in the His-Purkinje system with digitalis therapy.

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APPENDICES

APPENDIX A

Appointment Letter

CARDIOVASCULAR
PROGRAM PROJECT 45

Area Code 503 225-8592
45
Portland, Oregon 97201

UNIVERSITY OF OREGON

HEALTH SCIENCES CENTER

An appointment has been made for you in the Cardiology Conduction Clinic. This clinic is an offshoot of the Cardiology Clinic and deals only with patients having bundle branch block on their electrocardiogram. The bundle branch block shown on your EKG is not new. You are being asked to come to the clinic simply because you are part of the patient group in question.

Please report to the reception desk of the Family Practice Clinic Building between 8:30 - 9:00 am, Wednesday,_____. There will be no charge for this visit which involves an EKG and a short physical exam.

If the enclosed appointment time is agreeable, return the appointment card by mail at our expense. If, for any reason, the appointment cannot be kept, please let us know.

Sincerely,

Patricia A. Golden, Research Asst.
Susan Kauffman, R.N.
Cardiac Conduction Clinic, 225-8753

Enc.

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APPENDIX B

Consent Form for the Use of Ouabain in His Bundle Studies

CONSENT FORM FOR THE USE OF OUABAIN IN HIS BUNDLE STUDIES

I, _____, agree to be included in the study evaluating the effects of ouabain on the electrical conduction system in the heart.

I understand that the study will include the following:

(a) Under local anesthesia, veins will be located by a needle puncture or small incision on my arms and groins and through these, wires will be advanced into my heart.

(b) Electrocardiogram tracings will be recorded from the wires in the heart and the heart will then be electrically paced, that is, made to go faster, while repeat measurements are made. This is called a HIS Bundle Study.

(c) Ouabain, a drug generally used to affect the heart's electrical conduction system and/or the strength of the heart beats, will then be given by vein and after a waiting period of 45 minutes, the measurements and pacing will be repeated.

(d) Following the measurements, the wires will be removed and a pressure bandage will be applied to the needle sites and/or the small incisions will be sutured.

I understand that the risks of the procedure and the discomfort are minimal but could include the following:

(1) Bleeding from the needle puncture site or blockage of the vein used. The former will be treated by reapplying pressure and though the latter could cause clots to form, in most instances there are no bad consequences.

(2) Abnormal heart rhythms could develop from the wires in the heart, the electrical pacing, or the ouabain. These will be treated appropriately with medicines, a different type of heart pacing or if necessary with an extended electrical shock.

(3) Chest pain may develop from the pacing. Should this occur the pacing will be discontinued.

The procedure and its potential risks have been carefully explained to me to my full satisfaction. I understand that the ouabain will be used for investigational purposes and that I will not benefit from its use. I understand the purposes of the HIS Bundle study with ouabain and understand that I am free to withdraw from the study at any time and a decision to do so will in no way adversely affect my medical care.

Knowing the above I agree to participate in the study,

Signed_____

Date _____

Witness_____

Date _____

APPENDIX C

Clinical Data on the 48 Patients in Groups A,B,C and D

Clinical Data on 8 Patients With
Bi- or Trifascicular Disease

GROUP A

Patient Number	Age & Sex	Associated Cardiovascular Diseases or Symptoms	ECG Pattern
1	76 M	CAD	LBBB, 1^{O}AV
2	60 M	CHF	RBBB, LAD
3	58 F	VALVE	RBBB, LAD, 1^{O}AV
4	45 F	CAD, HTN	LBBB, 1^{O}AV
5	64 M	CAD	RBBB, LAD
6	85 M	CAD	LBBB, LAD
7	65 M	NONE	LBBB, LAD
8	68 M	CAD, HTN	LBBB, 1^{O}AV

CAD, coronary artery disease; CHF, congestive heart failure; HTN, hypertension; VALVE, valvular heart disease; LBBB, left bundle branch block; RBBB, right bundle branch block; 1^{O}AV, first degree atrioventricular block; LAD, left axis deviation; F, female; M, male; Age in years

Clinical Data on 10 Patients With
Normal Intraventricular Conduction

GROUP B

Patient Number	Age & Sex	Associated Cardiovascular Diseases or Symptoms	ECG Pattern
1	72 M	CHF	Normal
2	35 M	Palpitation	Normal
3	81 M	CAD	1^{O}AV, IMI
4	54 M	CAD	IMI
5	65 M	CAD	AMI
6	76 M	CAD	1^{O}AV, LAD
7	70 M	CAD	IMI, AMI
8	72 F	PAT	1^{O}AV
9	75 M	CHF	Normal
10	86 M	Bradycardia	1^{O}AV

CHF, congestive heart failure; CAD, coronary artery disease; PAT, paroxysmal atrial tachycardia; 1^{O}AV, first degree atrio-ventricular block; IMI, inferior myocardial infarction; AMI, anterior myocardial infarction; LAD, left axis deviation

Clinical Data on 17 Patients With Bifascicular Disease

GROUP C

Patient Number	Age & Sex	Associated Cardiovascular Diseases or Symptoms	ECG Patterns
1	76 M	CAD	RBBB, LAD
2	60 F	CAD	LBBB
3	58 F	CHD	RBBB, RAD
4	65 M	CAD	RBBB, LAD, 1^{O}AV
5	69 F	NONE	RBBB, LAD, 1^{O}AV
6	72 F	CAD, HTN	LBBB
7	74 M	CAD	RBBB, LAD
8	77 M	NONE	RBBB, LAD, 1^{O}AV
9	48 M	HTN	RBBB, LAD
10	79 M	NONE	RBBB, LAD
11	66 M	CAD	RBBB, LAD
12	49 F	HTN	RBBB, LAD
13	95 M	CAD	RBBB, LAD, 1^{O}AV
14	74 M	CAD	RBBB, RAD, 1^{O}AV
15	63 M	CAD	RBBB, LAD
16	67 M	CAD	RBBB, LAD
17	77 F	NONE	RBBB, LAD

CAD, coronary artery disease; CHD, congenital heart disease; HTN, hypertension; RBBB, right bundle branch block; LBBB, left bundle branch block; 1^{O}AV, first degree atrioventricular block; LAD, left axis deviation; RAD, right axis deviation

Clinical Data on 13 Patients With
Trifascicular Disease

GROUP D

Patient Number	Age & Sex	Associated Cardiovascular Disease or Symptoms	ECG Pattern
1	72 F	NONE	RBBB, LAD, 1^{o}AV
2	51 F	VALVE	RBBB, LAD
3	62 M	VALVE	RBBB, RAD, 1^{o}AV
4	45 F	NONE	LBBB
5	70 M	CAD	RBBB, 1^{o}AV
6	49 M	CAD	RBBB, RAD, 1^{o}AV
7	64 M	CAD	RBBB, LAD
8	77 F	HTN	RBBB, LAD, 1^{o}AV
9	67 M	CAD	RBBB, LAD
10	69 M	CAD	RBBB, RAD, 1^{o}AV
11	84 F	CAD	LBBB
12	53 M	CAD, HTN	LBBB
13	76 F	HTN	LBBB

VALVE, valvular heart disease; CAD, coronary artery disease; HTN, hypertension; RBBB, right bundle branch block; LBBB, left bundle branch block; 1^{o}AV, first degree atrioventricular block; LAD, left axis deviation; RAD, right axis deviation

APPENDIX D

Electrophysiologic Data on the 48 Patients in Groups A,B,C, and D

Electrophysiologic Data on 8 Patients
With Bi- or Trifascicular Disease

GROUP A

Patient Number	Heart Rate		Intervals (msec)								Heart Rate at Wenckebach	
			PA		AH		HV		SNRT			
	C	1H	C	1H	C	1H	C	1H	C	1H	C	1H
1	70	71	59	71	69	46	74	70	--	--	--	--
2	92	85	54	49	63	57	60	65	--	--	--	--
3	70	60	30	55	90	65	65	70	--	--	--	--
4	67	67	25	39	125	112	80	70	--	--	--	--
5	60	80	--	--	79	90	61	59	--	--	--	--
6	66	64	70	77	90	87	70	67	--	--	--	--
7	80	83	--	--	36	31	59	51	--	--	--	--
8	78	72	--	--	105	105	63	62	--	--	--	--

C, control; 1H, 1 hour later

Electrophysiologic Data on 10 Patients
With Normal Intraventricular Conduction

GROUP B

Patient Number	Heart Rate		Intervals (msec)								Heart Rate at Wenckebach	
			PA		AH		HV		SNRT			
	C	O	C	O	C	O	C	O	C	O	C	O
1	85	98	28	43	124	148	32	32	890	--	none	none
2	70	68	21	23	63	64	46	43	1020	950	140	120
3	78	74	40	42	160	350	51	53	1260	--	90	76
4	70	65	34	22	78	111	54	51	1029	948	150	114
5	70	76	50	59	112	112	51	50	900	840	152	150
6	53	50	11	15	127	217	49	48	1550	1140	122	113
7	59	54	04	04	109	77	44	39	--	--	--	--
8	80	70	85	80	55	68	48	48	--	--	--	--
9	82	98	48	--	76	--	47	45	--	--	--	--
10	51	47	51	50	217	227	51	47	1606	1061	99	100

C, control; O, Ouabain

Electrophysiologic Data on 17 Patients
With Bifascicular Disease

GROUP C

Patient Number	Heart Rate		Intervals (msec)								Heart Rate at Wenckebach	
			PA		AH		HV		SNRT			
	C	O	C	O	C	O	C	O	C	O	C	O
1	--	--	70	89	148	--	46	36	--	--	--	--
2	76	60	22	27	85	93	47	45	1050	1140	120	120
3	90	96	55	65	65	75	50	52	940	936	--	--
4	80	78	60	59	136	119	48	45	950	1500	111	91
5	85	84	20	35	115	130	50	51	--	--	--	--
6	90	92	95	82	87	101	50	55	1155	1085	150	130
7	--	--	33	--	77	65	46	47	1280	--	--	--
8	88	89	18	20	115	216	46	47	930	1100	98	40
9	80	86	--	--	125	130	40	40	1130	935	--	--
10	52	56	--	40	74	80	53	52	965	1060	--	--
11	93	94	18	51	67	96	52	48	800	580	176	152
12	52	60	55	65	65	70	50	52	940	936	--	--
13	75	78	50	40	115	130	47	53	975	625	--	--
14	85	83	--	--	109	86	43	49	900	--	--	--
15	78	75	26	49	97	85	35	30	911	930	--	--
16	67	60	39	37	85	86	45	37	1179	1050	155	154
17	66	59	20	20	72	83	42	43	1275	1265	--	150

C, control; O, Ouabain

Electrophysiologic Data on 13 Patients
With Trifascicular Disease

GROUP D

Patient Number	Heart Rate		Intervals (msec)								Heart Rate At Wenckebach	
			PA		AH		HV		SNRT			
	C	O	C	O	C	O	C	O	C	O	C	O
1	69	75	57	51	66	84	74	70	--	--	152	120
2	70	72	18	25	102	78	75	73	1242	2113	153	131
3	67	63	36	46	83	119	66	60	--	--	--	--
4	--	--	25	20	105	130	56	60	1162	--	--	--
5	63	61	45	38	155	164	56	62	1477	--	121	121
6	86	65	38	39	134	149	79	80	910	660	--	--
7	74	75	52	65	100	124	63	61	1030	1150	--	--
8	78	72	21	24	118	130	81	74	785	780	110	110
9	79	77	40	27	115	130	74	75	915	--	74	110
10	--	--	75	75	120	173	71	69	1122	700	--	143
11	74	70	55	35	60	75	58	57	885	1045	176	170
12	72	86	20	27	115	108	56	58	962	805	--	--
13	62	61	40	44	101	120	56	57	1066	--	130	--

C, control; O, Ouabain

AN ABSTRACT OF THE CLINICAL INVESTIGATION OF

SUSAN M. KAUFFMAN

For the Master of Nursing

Date of receiving this degree:

Title: DIGITALIS IN BI- AND TRIFASCICULAR DISEASE: ITS EFFECT ON THE HV INTERVAL

Approved: [redacted]

(Clinical Investigation Adviser)

Patients with disease of the His-Purkinje tissue, i.e., bi- or trifascicular disease (BTD), are presume to be at higher risk of developing complete heart block (CHB), than patients with normal intraventricular conduction. Digitalis therapy has also been shown to precipitate CHB in certain patients. Frequently, patients with BTD require digitalis therapy for management of associated cardiovascular disease. Although digitalis does not prolong His-Purkinje conduction time, (quantitated by the HV interval), in patients without conduction defects; the effect of ouabain a fast acting digitalis glycoside, on patients with compromised ventricular conduction has not previously been reported.

Electrophysiological studies were performed in 48 patients. After baseline recordings were obtained, ouabain (OU) (0.015 mg/kg) was given introvenously and recordings were repeated in 45 minutes. Group A, 8 patients with BTD not given OU, served as controls to demonstrate the effect of the procedure on conduction times. Ten patients, Group B, were controls with normal electrocardiograms. Group C, 17 patients, had bifascicular disease, defined by the surface electrocardiogram (ECG) and a normal HV interval (HV $\leq$ 55 msec). Thirteen patients, Group D, demonstrated trifascicular disease, a prolonged HV time at rest (HV $>$ 55 msec).

No significant change of the HV interval with time occurred in Group A, the 8 patients not receiving OU ($p > .05$). Also, OU did not alter HV conduction in Group B ($p > .05$). The mean HV interval (mean SEM in msec) for Group C, bifascicular disease, was 46 ± 1.3. This mean changed to 47 ± 1.6 after OU ($p > .05$). The HV interval decreased in 7 cases (4.7 ± 1.3), increased in 9 (2.8 ± 7.4), and remained the same in one. For Group D, trifascicular disease, the mean interval was 66 ± 2.8 changing to 66 ± 2.2 ($p > .05$) after OU. HV time decreased in 7 instances

(3.4 $\pm$ 0.9) and increased in 6 (3.2 $\pm$ 1.0). Also, the HV interval pre-OU (55 $\pm$ 2.2) was not significantly different from the post-OU valued (55 $\pm$ 2.3) for Groups C and D combined, the patients with BTD ($P > .05$). Heart rate. PA interval, sinus node recovery time, and level of Wenckebach pre - and post-OU did not change ($p > .05$) in any of the four groups. However, in the 30 patients with BTD, Groups C and D, the AH interval showed a significant increase ($p < .01$) from 99 $\pm$ 4.7 pre-OU to 111 $\pm$ 6.5 post-OU.

Although OU increased HV time in 15 of 30 patients with BTD, it also decreased HV conduction in fourteen. In either case, the variation of the resting HV interval pre- vs. 45 minutes post-OU was not statistically significant. The patients with BTD in this study group did not significantly increase His-Purkinje conduction time with digitalis therapy.