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## Dromotropic Influences of the Individual Cardiac Nerves at the Atrioventricular Junction of the Canine Heart

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DROMOTROPIC INFLUENCES OF THE INDIVIDUAL CARDIAC  
NERVES AT THE ATRIOVENTRICULAR JUNCTION  
OF THE CANINE HEART

by

Lynn E. Rinkema

A Thesis Submitted to the Faculty of the Graduate School  
of Loyola University of Chicago in Partial Fulfillment  
of the Requirements for the Degree of  
Master of Science  
September  
1980

## VITA

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Lynn is a student member of the American Physiological Society.

Her publications include the following:

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2. Randall, W.C., L.E. Rinkema, and S.B. Jones. Atrial overdrive suppression in the conscious dog in the presence and absence of the Keith-Flack Node. Fed. Proc. 39: 1083, 1980.
3. Rinkema, L.E., J.X. Thomas, and W.C. Randall. Effect of right vs. left stellate stimulation on regional coronary blood flow in the dog. Physiologist 23(4): 78, 1980.

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## INTRODUCTION

Initial studies of the canine cardiac nerves were anatomical in nature and appeared in the literature as early as 1893 with their description by Keng (13). Keng's basic account has remained virtually unchanged over the years although further anatomical detail was added by Schurawlew (31), Nonidez (23), Mizeres (18), and McKibben and Getty (16). However, Mizeres attempted to correlate the structure and function of the canine cardiac nerves and his nomenclature has become well established in the literature. Although he encountered some variability in the anatomical location of specific nerves, he was able to conclude that "the canine cardiac nerves are not a haphazard tangle of structures interdigitating with one another, but discretely organized structures which are generally consistent from one animal to another" (18). The functional studies of Mizeres (19,20) focused on the cardiac nerves containing cardioinhibitory and cardioacceleratory fibers. Thus, he described the innervation patterns of the sinoatrial node.

Correlation of structure-function relationships took another step forward in 1968 when Randall et al. (27) showed that individual cardiac nerve stimulation could change the inotropic state in highly localized areas of the heart. Kralios et al. (14) demonstrated that this localization also applied to ventricular refractory period changes produced by cardiac nerve stimulation.

Thus, it has been shown that the individual cardiac nerves innervate localized areas of the atria (such as the sinoatrial node) and

the ventricles to produce differential functional changes. This study seeks to extend this line of investigation by examining the distribution and functional autonomic composition of the canine cardiac nerves to the atrioventricular (A-V) junctional region.

## LITERATURE REVIEW

### A. Extracellular Recording Techniques for Measurement of Atrioventricular Conduction and Electrical Activity.

Early measurements of atrioventricular electrical activity were made in isolated, perfused hearts in which an incision was made in the right atrium to expose the interatrial septum for placement of recording electrodes. Utilizing this type of preparation Alanis et al. (1) described the nature of electrical activity recorded from the anatomical location of the His bundle. The sharp, well-defined deflection recorded over this area has become a landmark in atrioventricular conduction recordings and is used to define two discrete intervals. The A-H interval is the conduction time from the inferior atrium to the His bundle and the H-V interval is the conduction time from the His bundle to the ventricular muscle.

Scher et al. (32) also used a modification of this technique to study conduction velocities in various portions of the atrioventricular junctional region. Thus, this technique has been very useful for correlating structure and function in the atrioventricular conducting system.

In 1960 Hoffman et al. (10) described an electrode suitable for chronic implantation. While the dog was on cardiopulmonary bypass, the electrode was placed over the junctional region through an atriotomy and sutured in place. The atrial incision and thoracotomy were then closed and the animal allowed to recover. Because of the difficulty in defining the precise anatomical location of the His bundle, the electrode contained

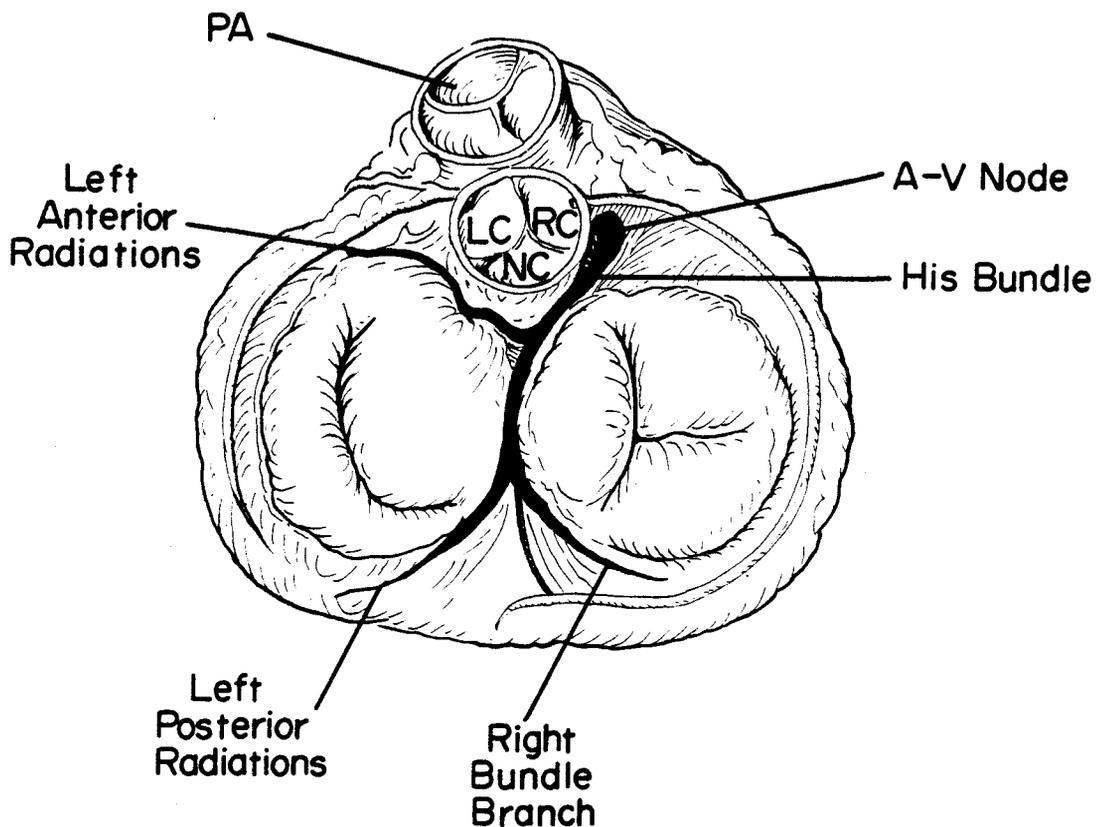
five contact points. The two contacts which provided the best bipolar recording of His bundle activity were located by trial and error and used in making the recordings.

The development of extracellular recording techniques suitable for clinical use began in 1968 with a report by Scherlag, Helfant and Damato (33). These investigators constructed a thin catheter of fairly rigid material which contained three electrode bands placed along the catheter at 15-18 mm distances starting at the catheter tip. This catheter was passed into the right atrium via a femoral vein and the tip of the catheter was passed across the tricuspid valve. This procedure allowed the second pair of electrodes to be manipulated until they rested against the atrial septum in the area of the His bundle. However, the catheter was not anchored securely in place and therefore the recordings were often unstable. Stability of His bundle recording was improved by passing the electrode into the aortic root via the right carotid artery and wedging the tip of the catheter into the non-coronary cusp of the aorta (34). Figure 1 shows a cross-sectional view of the heart at the level of the aortic valve. The atrioventricular conducting system passes from the inferior interatrial septum (A-V node) toward the apex of the ventricles (the bundle branches). The His bundle lies near the non-coronary cusp (NC).

In 1975 Urthaler and James (38) compared the electrograms recorded from the aortic root with those recorded using a Hoffman type of electrode. They concluded that "a stable and accurate His bundle electrogram can be obtained from the aortic root and has the experimental advantage of not having to open the right atrium or place sutures near the A-V node".

FIGURE 1

## SCHEMATIC REPRESENTATION OF THE A-V CONDUCTION SYSTEM



This schema of a cross-sectional view of the heart at the level of the aortic valve demonstrates the anatomical relationship between the non-coronary cusp (NC) of the aorta and the His bundle. The atrio-ventricular conduction system passes from the anterior interatrial septum (A-V node) toward the apex of the ventricles via the right bundle branch and the anterior and posterior radiations of the left bundle branch. The His bundle lies in the plane of this schema immediately adjacent to the NC. LC=left coronary cusp, RC=right coronary cusp, PA=pulmonary artery.

## B. Heart Rate Effects on Atrioventricular Conduction.

It has been shown that as heart rate increases myocardial excitability recovers more rapidly. Siebens et al. (36) showed that in ventricular muscle this phenomenon was due to a shortening of the absolute refractory period. In addition, these investigators found that repolarization and the end of the total refractory period occurred simultaneously. Because recovery of excitability was complete before the next depolarization, conduction velocity was thought to be independent of heart rate.

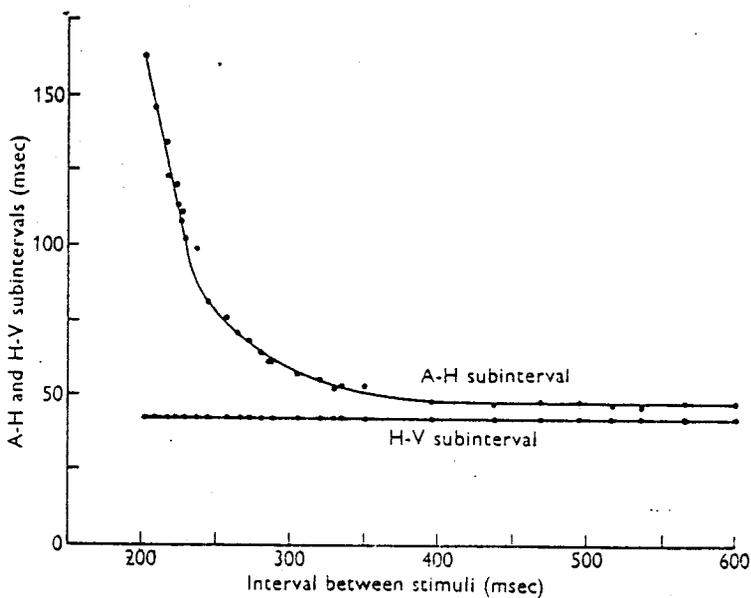
In contrast, increases in heart rate slow conduction velocity through the atrioventricular junctional region. Meredith, Mendez, Mueller, and Moe (17) demonstrated that in the N region of the A-V node the recovery of excitability was delayed well beyond the end of repolarization. This lag in recovery increased as pacing rate increased, resulting in decreased conduction velocity through the N region of the node.

Alanis et al. (1) showed that conduction velocity, as measured by the A-H interval, was independent of heart rate until the cycle length decreased to about 340 msec (heart rate=175 beats/min.). Presumably at rates below 175 beats/min cycle length did not encroach upon the A-V nodal refractory period. As cycle length decreased further, atrioventricular conduction velocity slowed, as indicated by the gradual lengthening of the A-H interval. At cycle lengths less than 200-220 msec (heart rate=275-300 beats/min) the rate at which conduction velocity slowed was accentuated (figure 2).

When the atrial cycle length is plotted against the resulting

FIGURE 2

## EFFECT OF CYCLE LENGTH ON A-H AND H-V INTERVALS



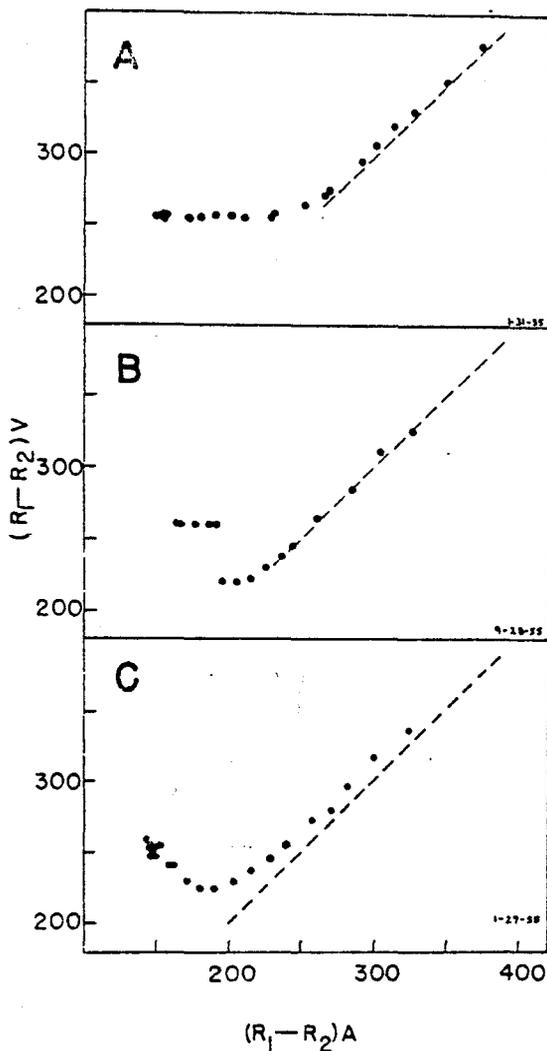
A-H interval (upper curve) increases as the interval between stimuli (cycle length) decreases below 340 msec. This increase has two components, a slow increase followed by a rapid increase as the interval between stimuli decreases below 200-240 msec. H-V interval is independent of changes in cycle length. (Taken from Alanis et al. (1)).

ventricular (V-V) or His bundle (H-H) cycle length slowing is indicated by a deviation from the line of identity. The results of a study by Moe, Preston and Burlington (21) plotted in this way (figure 3) are similar to those of Alanis et al. (1). Note that A-V conduction was independent of cycle length at cycle lengths greater than 340 msec and between cycle lengths of 340 and 200 msec they demonstrated three patterns of response; 1) an accentuated rate of conduction slowing (panels A and C of figure 3), 2) an abrupt jump to a longer A-V interval with a resulting 'gap' in conduction time (panel B) and 3) cessation of A-V conduction (A-V block) for one or more beats.

Martin (15) showed that a complex interaction occurs between vagal effects on heart rate and atrioventricular conduction. His study utilized brief (less than 40 msec) trains of vagal stimulation placed in various portions of the cardiac cycle to generate a time course of vagal activity (vagal effect curve). The change in A-V interval was measured during vagal stimulation in the paced and unpaced heart. In addition the changes in cycle length produced by vagal stimulation in the unpaced heart were stored in the memory of a digital computer. After crushing the sinoatrial node of the dog these sequences of changing cycle lengths were 'played back' in real time into pacing electrodes near the sinoatrial node and changes in A-V interval again determined. In this manner the atrioventricular conduction response to the applied sequence of cycle lengths could be assessed in the absence of the interacting effects of vagal stimulation. The responses of atrioventricular conduction to the cycle length playback were compared to the responses calculated by subtracting the responses in the paced

FIGURE 3

## EFFECT OF CYCLE LENGTH ON VENTRICULAR INTERVAL



Plot of the interval between basic and premature responses in the atria  $(R_1 - R_2)A$  in relation to the corresponding ventricular interval  $(R_1 - R_2)V$  in three different experiments (panels A, B and C). Conduction velocity was independent of cycle length for points falling on the line of identity (dashed line). This occurred at atrial intervals over 300 msec. At atrial intervals below 200 msec, three patterns of response are illustrated. Panel A: ventricular interval remains constant. Panel B: ventricular interval abruptly increases resulting in a gap. Panel C: ventricular interval slowly increases. (From Moe *et al.* (21)).

heart from those in the unpaced heart. If the curves had been similar it would have indicated a simple algebraic summation of heart rate and vagal effects on the atrioventricular junction. However, it was found that over some portions of the vagal effect curves, atrioventricular conduction decreased more when both vagal activity and changing cycle length were simultaneously imposed (unpaced minus paced curves) than when cycle length changes alone were imposed (playback). Thus, the atrioventricular conduction time was actually less in the presence of vagal activity than in its absence. Martin termed this the paradoxical response.

### C. General Neural Effects on Atrioventricular Conduction.

Autonomic nervous system control of the atrioventricular junctional region has been well characterized in general terms. Alanis et al. (1) were among the first to show that sympathetic activity facilitated atrioventricular conduction while parasympathetic activity attenuated it. Using the extracellular recording technique described above to record A-H and H-V intervals they found that epinephrine (4-30  $\mu\text{g}/\text{min}$ ) shortened the A-H and H-V intervals by 36% and 13%, respectively. Vagal stimulation and acetylcholine produced dose-dependent increases in A-H interval until block occurred, but no changes in H-V interval were observed.

Wallace and Sarnoff (39) measured conduction through the atrioventricular junction, Purkinje system, and ventricular muscle during an investigation into the cause of improved synchrony of ventricular contraction induced by sympathetic activity. Two Hoffman type electrodes, one over the His bundle and one in the right anterior papillary muscle,

were used to measure A-H interval and H-P interval. The H-P interval was the time between the deflections produced by activity in the His bundle and the Purkinje tissue of the papillary muscle. These intervals could be measured to an accuracy of 0.4 msec. Left stellate ganglion stimulation decreased the A-H interval in all of the 12 dogs tested. The average decrease was 31.1 msec, a 49.8% change. In 8 dogs the H-P interval was measured and left stellate stimulation decreased this interval by  $0.7 \pm 0.1$  msec (2.4%). Although this change was small it was statistically significant.

Spear and Moore (37) utilized brief, 100 msec trains of vagal or stellate stimulation to induce changes in atrioventricular conduction. Again A-H interval was altered during these manipulations, denoting a change in conduction through the A-V node. In 6 dogs in which the vagus was stimulated, the latency to the beginning of the conduction delay was 165-230 msec. The response rose rapidly to peak changes of 26-290% and returned to control values within .80-1.15 seconds. In contrast, the acceleratory response to stellate ganglion stimulation (N=4) had a latency of 1.0-1.5 seconds, rose slowly to a peak change of 14.5-29.5% and took 13-31 seconds to return to control. Thus, the vagal effect was larger than the stellate effect and ran its full course in the time necessary for stellate stimulation to begin to exert its effects. Although nerves from both right and left sides were stimulated, Spear and Moore saw no differences in their effects on conduction. However, this conclusion was based on observations in only two dogs for the left vagus and in only one dog for the left stellate ganglion. As another aspect of this study, Spear and Moore were unable to demonstrate any

changes in H-V interval with this type of nerve stimulation.

In a report published in 1973, Priola (25) examined the neural control of conduction in the atrioventricular junctional region and the main bundle branches. Hoffman type electrodes were placed over the His bundle, right bundle branch (RB) and left bundle branch (LB) for recording electrical activity in these structures. Control A-H intervals before right and left stellate nerve stimulations were  $53 \pm 2$  and  $52 \pm 2$  msec, respectively. Right stellate stimulation was shown to decrease A-H interval by  $26 \pm 2\%$  in 20 dogs, while left stellate stimulation decreased A-H interval by  $31 \pm 4\%$  in 13 dogs tested. Administration of blocking doses of practolol or propranolol eliminated these changes. Neither the H-RB nor the H-LB intervals were found to change with stellate stimulation or beta blockade from their prestimulation control values of  $15 \pm 1$  msec.

Thus, although the effects of autonomic activity on the A-H interval are well established, controversy exists in the literature concerning the effects of sympathetic stimulation on conduction in the Purkinje system. Alanis et al. (1) reported a 13% decrease in H-V interval and Wallace and Sarnoff (39) reported a 2% decrease in H-P interval. However, Spear and Moore (37) and Priola (25) reported no change in H-V interval with sympathetic stimulation.

#### D. Differential Neural Effects on the Atrioventricular Junction.

In 1971 Irisawa et al. (12) compared the effects of right and left vagal stimulation on heart rate and atrioventricular conduction in the unpaced dog heart. Stimulation of the left vagus at 7-10 Hz, 0.5 msec duration and minimal voltage increased the cycle length an average of

19.5% and the A-V interval an average of 17%. Stimulation of the right vagus at similar stimulus parameters caused the cycle length to increase 34.5% compared to a 5.5% increase in A-V interval. Repeating the stimulations for the left and right stellate ganglia at 10 volts demonstrated that left stellate ganglion stimulation decreased the cycle length by 3.3% and the A-V interval by 16.5%, while right stellate stimulation decreased cycle length and A-V intervals by 32.2% and 7.3%, respectively. In general, Irisawa et al. (12) noted that nerves of the right side had a greater effect on heart rate than on atrioventricular conduction, while the reverse was true for the nerves of the left side. Unfortunately, the variability in results and the small number of experiments (N=4) made the generalizations drawn by these workers tenuous.

Goldberg and Randall (8) reviewed the concept of differential dromotropic effects of the right and left stellate ganglia and performed additional experiments to examine this question. In addition to measuring A-V junctional conduction with a Hoffman electrode, bipolar electrodes were placed in each of the internodal pathways for measurements of atrial conduction. Pacing was accomplished using a sinus node electrode. Neither right nor left stellate stimulation changed atrial conduction time or the H-V interval. However, left stellate stimulation decreased the A-H interval by 35% in the unpaced preparation, while right stellate stimulation decreased this interval by only 9%. During pacing, a 27% shortening in A-H interval was observed with left stellate stimulation, while A-H interval decreased 17% during right stellate stimulation. These differences in the effects of right and left stellate stimulation were highly significant ( $p < .001$ ). These results also

illustrated the importance of maintaining a constant heart rate.

Several studies have examined the effects of individual cardiac nerve stimulation on the atrioventricular junctional region. The earliest, and most comprehensive study was the study by Geis et al. (7). In this study individual cardiac nerves were stimulated before and after each of nine paracardiac surgical procedures. The elimination of responses was used to describe the anatomical pathways for input to the A-V junction. If atrial contraction and electrical activity occurred at the same time or following ventricular activity and contraction, the A-V node was designated as the site of origin of the rhythm. An increase in the rate of this rhythm (A-V tachycardia) produced by nerve stimulation was used as evidence of sympathetic innervation of the atrioventricular junction by that nerve. When stimulation caused no change in atrial rate but slowing of the ventricular rate or complete ventricular arrest, the response was interpreted as cholinergic innervation of the A-V node (A-V bradycardia). These responses could only be elicited following denervation of the sinus nodal region. The results are presented in table 1. Although this study examined the effects of all of the cardiac nerves on the atrioventricular junctional region, the results are neither complete nor conclusive. The criteria used to identify an A-V junctional rhythm, although the best that could be realized from electrocardiographic data, were not very sensitive. In addition, neural pathways to the sinoatrial node had to be eliminated in order to reveal A-V nodal changes and some A-V nodal innervation (especially that from the right side) may have been eliminated. Finally, no attempt was made in these studies to determine if any of the nerves examined contained a mixture of both

TABLE 1

## EFFECT OF CARDIAC NERVE STIMULATION ON ATRIOVENTRICULAR RATE

<u>NERVE STIMULATED</u>	<u>A-V TACHYCARDIA*</u>	<u>A-V BRADYCARDIA*</u>
Left anterior ansa subclavia	11	0
Left posterior ansa subclavia	8	0
Innominate cardiac nerve	2	0
Ventromedial cardiac nerve	3	0
Ventrolateral cardiac nerve	11	0
Left thoracic vagus	0	11
Right anterior ansa subclavia	7	0
Right posterior ansa subclavia	6	0
Right recurrent cardiac nerve	2	1
Craniovagal cardiac nerve	2	2
Caudovagal cardiac nerve	1	4
Right thoracic vagus	0	11

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\* Number of animals exhibiting this response out of a total of 11. (From Geis et al. (7)).

sympathetic and parasympathetic fibers by using adrenergic and cholinergic blocking agents.

Dromotropic effects of two individual cardiac nerves, the right recurrent cardiac nerve and the ventrolateral cardiac nerve, were examined in greater detail by Fishman et al. (4). These workers noted that stimulation of the right recurrent cardiac nerve significantly decreased the functional and effective refractory periods of the atrioventricular junction (indicating a sympathetic component) while transection of this nerve increased these refractory periods in the anesthetized, open chest preparation (indicating the presence of sympathetic tone). In addition, stimulation of the ventrolateral cardiac nerve decreased the functional and effective refractory periods but nerve transection had no effect on these parameters. Thus, Fishman et al. concluded that the ventrolateral cardiac nerve carries sympathetic input to the atrioventricular junction but does not carry tonic activity. In a subsequent study Fishman (5) showed that ventrolateral cardiac nerve stimulation increased the maximal atrial pacing rate at which one-to-one atrioventricular conduction occurred. However, no attempt was made in either study to determine whether the right recurrent or ventrolateral cardiac nerves contained both parasympathetic and sympathetic fibers.

Thus, it has been definitively shown that heart rate and autonomic activity change atrioventricular conduction characteristics. Sympathetic activity accelerates conduction, while parasympathetic activity and heart rate slow it. These changes occur predominately in the A-H interval indicating a role of the A-V node in conduction velocity changes. The actions of the autonomic nervous system on the dromotropic properties of

the Purkinje system (H-V interval) are less clear.

Differential patterns of innervation to the atrioventricular junction by the individual cardiac nerves have also been studied (4,5,7). These studies have been either incomplete (only one or two nerves studied or no autonomic blocking agents given) or inconclusive (possible surgical interruption of pathways to the A-V junction or less sensitive methods of measurement).

The present study systematically studied the effects of cardiac nerve stimulation on atrioventricular conduction. The His bundle catheter technique (34), a sensitive indicator of changes, was utilized to make direct measurements of atrioventricular conduction time. Blocking agents were utilized to unmask hidden functional effects in nerves that potentially could have a mixed autonomic composition.

## METHODS

### A. The Surgical Preparation.

Sixteen adult mongrel dogs, unselected for sex and weighing between 14 and 25 kg, were used in this study. Twelve dogs were anesthetized with sodium pentobarbital (30 mg/kg, iv.) while the other four animals received 0.3-0.5 ml of Innovar iv. (0.4 mg/ml fentanyl, 20 mg/ml droperidol) followed 15-20 minutes later by alpha chloralose (60-80 mg/kg, iv.). Saline was used as a vehicle for the alpha chloralose. A midline cervical incision was made for isolation of the left and right cervical vagi and the right carotid artery. The trachea was cannulated and the animal ventilated with an oxygen enriched air mixture using a Bird Mark 7 respirator. Fluid filled, polyethylene catheters were inserted into a femoral artery for recording arterial pressure and into a femoral vein for drug and fluid administration. Arterial pressure and lead II EKG were monitored throughout the procedure on a Grass polygraph. Decamethonium (10 mg, iv.), a depolarizing muscle relaxant, was given prior to a bilateral thoracotomy through the third intercostal space on the right side and through the fourth intercostal space on the left side. The sternum and internal mammary arteries were left intact. This procedure provided good exposure of the cardiac nerves while limiting trauma. A 1-2 cm slit was made in the pericardium through which a bipolar plaque electrode was sewn to the right atrial appendage. The electrode was used to pace the heart at 200 beats per minute, thus eliminating changes in atrioventricular conduction due to alterations

in heart rate.

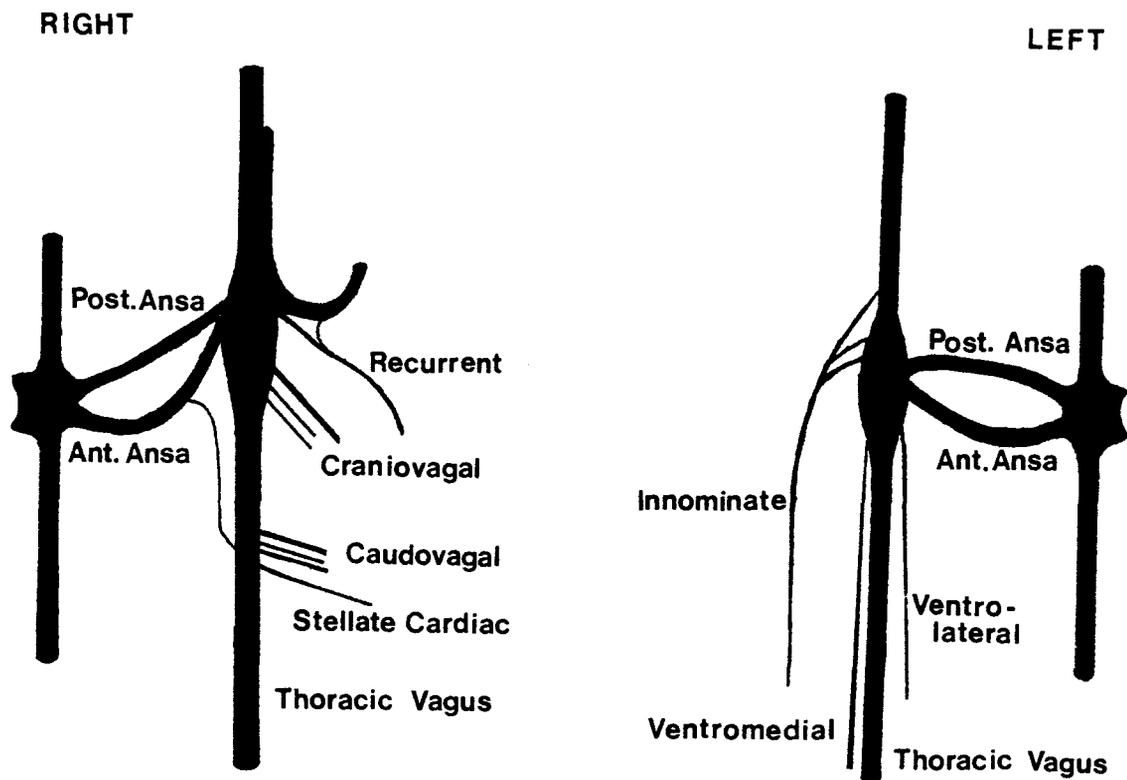
The individual cardiac nerves on both sides were dissected free from surrounding tissue, identified, looped with a piece of 4-0 silk, and bathed in mineral oil. Figure 4 is a schema of the anatomical locations of each of the cardiac nerves and their identities as used in this study. The nomenclature is that of Mizeres (18). Mizeres described two other nerves on the left side, the left stellate cardiac nerve and the dorsal cardiac nerve. However, they were not routinely seen and therefore were not included in this study. Following cardiac nerve identification and isolation, the heart was neurally decentralized by transection of the cervical vagi and the anterior and posterior ansa subclavia bilaterally.

#### B. Electrical Recordings.

Two bipolar plunge electrodes were used to record reference electrograms. The electrodes were constructed by threading two Teflon coated stainless steel wires (.005 in) through a 21 gauge needle and bending their tips to form a hook. The Teflon coating was stripped from the first 1-2 mm of wire to increase the area of electrode contact with the myocardium. One electrode was positioned in the left atrial appendage through a small slit in the pericardium. The second electrode was plunged directly through the pericardium into the left ventricular free wall. The electrode was positioned in the base of the left ventricle just lateral to the left anterior descending coronary artery, 1-2 cm below the circumflex artery. The electrical activity was amplified using a Grass P-511 amplifier with high input impedance. Low and high half amp frequency settings were 35 Hz and 30 KHz, respectively. The electrograms were displayed simultaneously on a Grass polygraph and

FIGURE 4

## SCHEMATIC REPRESENTATION OF INDIVIDUAL CARDIAC NERVE ANATOMY



This schema illustrates the relative anatomical locations of the individual cardiac nerves investigated in this study. The nomenclature used in this figure and throughout this study is that of Mizeres (18). (Ant.=anterior or ventral; Post.=posterior or dorsal).

on a cathode ray storage oscilloscope (Tektronics Model 5111). The oscilloscope was triggered to sweep from the pacing stimulator (Haer Pulsar 4i), and electrograms were recorded at a sweep speed of 20 msec per division.

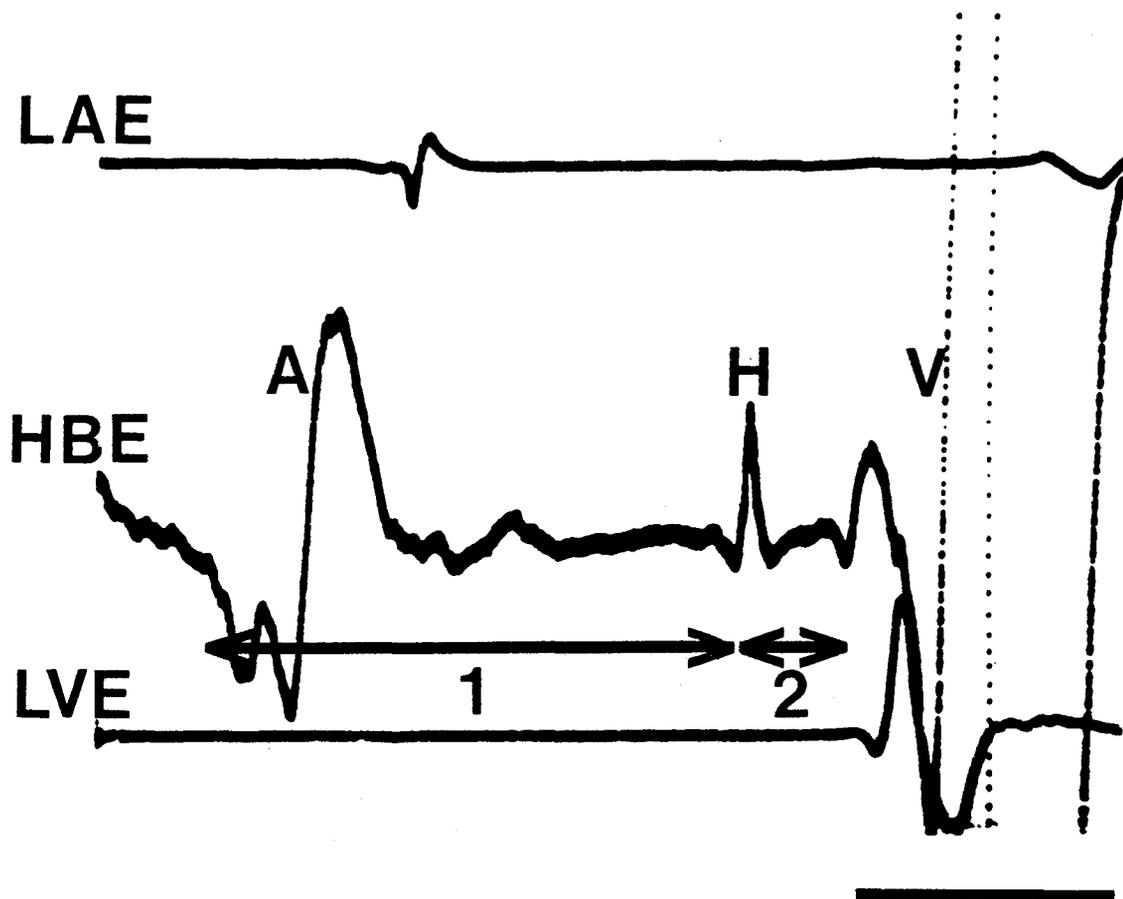
A His bundle electrode catheter was inserted into the right carotid artery, passed down into the ascending aorta, and the catheter tip was wedged into the non-coronary cusp of the aorta, according to the technique of Scherlag et al. (34). The His bundle catheters used in this study were tripolar in nature with interelectrode distances of 1 cm. The first electrode band was located at the catheter tip. A bipolar electrogram, recorded from the distal two electrodes, was amplified, filtered, and displayed in the same manner as the reference electrograms described earlier. Figure 5 is a photograph (Polaroid-Land Camera model C-5B) of an oscilloscope sweep. The traces, from top to bottom, were recorded from the left atrium, His catheter, and left ventricular base. Three deflections are present in the His catheter trace. These are designated 'A', 'H' and 'V' as they represent activity in the inferior Atrium, His bundle and Ventricular septum, respectively. His bundle catheter placement was considered correct when a stable, sharply peaked H deflection was recorded 25-45 msec before a V deflection. Scherlag et al. (35) showed that deflections occurring at shorter intervals were arising in the proximal bundle branches. Once the electrode catheter was properly positioned the recording remained stable over the entire time course of the protocol.

### C. The Protocol.

Fifteen to twenty minutes were allowed following the surgical

FIGURE 5

OSCILLOSCOPE SWEEP ILLUSTRATING HIS BUNDLE ELECTROGRAM MEASUREMENTS



The oscilloscope sweeps recorded in this study contained three traces recorded from the left atrium (LAE), His bundle catheter (HBE) and the left ventricular base (LVE). In the HBE three deflections occur which represent electrical activity in the inferior atrium (A), His bundle (H) and ventricular septum (V). A-H interval (1) is measured from the rapid component of the A wave to the start of the H wave. H-V interval (2) is measured from the start of the H wave to the fast component of the V wave. Time calibration (right lower corner) = 50 msec.

procedure for recorded parameters to reach a steady state. During this time supplemental doses of anesthetic or decamethonium were administered if needed.

The cardiac nerves were stimulated in random sequence using the parameters 10 Hz, 5 msec duration, 6 volts. Stimulation of all nerves on one side of the preparation was accomplished before moving to the other side. This procedure decreased the probability of dislodging the His catheter due to minor repositioning of the animal necessary when switching sides for nerve stimulation. The initial side of stimulation was also selected randomly. An oscilloscope sweep of the electrograms was photographed before each nerve stimulation and five seconds after onset of stimulation. Stimulation of the nerves, especially those on the right side, for longer than 5 seconds often resulted in a heart rate which exceeded the pacing rate of 200 beats per minute. Instead of increasing the pacing rate it was decided to limit the period of stimulation to 5 seconds. Although A-H and H-V intervals returned to control values within 10-15 seconds after cessation of stimulation, at least one minute was allowed between nerve stimulations. Following stimulation of each of the eleven cardiac nerves described (the anterior and posterior ansae subclavia were stimulated simultaneously) blocking doses of either atropine (0.4 mg/kg) or propranolol (1 mg/kg) were given. Five minutes later, the nerve stimulations and recordings were repeated.

The sixteen experiments performed in this study can be divided into three groups based upon the combination of anesthetic and blocking agent used. Eight dogs received sodium pentobarbital and propranolol,

four received sodium pentobarbital and atropine, and four received alpha chloralose and atropine.

#### D. A-H and H-V Interval Measurements.

Atrioventricular conduction time can be measured from the His bundle electrogram. The three distinct deflections seen in this recording divide the trace into two discrete intervals: the A-H interval (conduction time from the inferior atrium to the His bundle) and the H-V interval (conduction time through the His bundle and ventricular Purkinje system). The A-H interval is measured from the beginning of the fast component of inferior atrial activity (A wave) to the upstroke of the His bundle potential (H wave). The H-V interval is measured from the start of the H wave to the initial fast component of the V deflection. A sample of this procedure is shown in figure 5. These intervals could be measured with an accuracy of  $\pm 2.5$  msec.

Since the parasympathetic nervous system has been shown to slow conduction through the atrioventricular junctional region, an increase in either the A-H or H-V interval with neural stimulation was taken as evidence of parasympathetic innervation of the inferior atrium-His bundle region or the His bundle-Purkinje system, respectively. Similarly, since the sympathetic nervous system accelerates conduction, a decrease in either interval was taken as evidence of sympathetic innervation.

#### E. Statistical Analysis.

Variance between control values for the three groups of animals and for the individual cardiac nerves was tested for significant differences using an analysis of variance and Scheffe test. Differences between the control A-H or H-V intervals and those following stimulation

for each of the cardiac nerves were tested for significance using either a paired Student's t-test or a correlated Wilcoxin t-test (for nerves whose stimulation produced one or more cases of A-V block). Variances and differences were considered to be significant when  $p < .05$ .

## RESULTS

### A. Pre-stimulation Parameters.

The control measurements for the three groups of dogs are presented in Table 2. Heart rate following neural decentralization was similar in all groups of dogs. Mean arterial pressure was also similar in the three groups although tending to be lower in the chloralose anesthetized dogs.

Prior to administration of the selected blocking agent, the A-H interval was not significantly different between the three groups of animals. The mean A-H interval for the 16 dogs studied was  $74.8 \pm 4.6$  msec ranging from 45 to 105 msec. Following administration of the blocking agent the A-H intervals were significantly different ( $p < .05$ ) between the group of dogs anesthetized with chloralose and receiving atropine and the dogs receiving propranolol. However, no other significant differences between the means of the three groups were found, nor were any of the mean A-H intervals following blocker different from the mean intervals before blocker for a given group. There were no significant differences in H-V interval between the three groups, either before or after drug administration.

Since there were no significant differences between the control parameters or between the changes in response to nerve stimulation for the two groups of dogs which received atropine, the data from these groups were combined in subsequent analyses.

TABLE 2

## CONTROL HEMODYNAMIC AND CONDUCTION PARAMETERS

GROUP	HEART RATE (bpm)	MEAN ARTERIAL PRESSURE (mm Hg)	A-H INTERVAL (msec)		H-V INTERVAL (msec)	
			BEFORE BLOCKER	AFTER BLOCKER	BEFORE BLOCKER	AFTER BLOCKER
Atropine- Chloralose (N=4)	133 ± 15	94 ± 8	59.8 ± 5.4	63.4 ± 4.8	29.6 ± 4.6	29.6 ± 4.1
Atropine- Pentobarbital (N=4)	133 ± 7	110 ± 19	78.4 ± 13.0	81.3 ± 13.4	30.8 ± 4.1	31.9 ± 4.0
Propranolol- Pentobarbital (N=8)	131 ± 5	111 ± 6	80.4 ± 5.3	100.9 ± 7.0*	31.3 ± 1.4	32.5 ± 1.6

\*Significantly different ( $p < .05$ ) from similar measurements for the Atropine-Chloralose group. Values shown are the mean ± the standard error of the mean.

### B. Changes in H-V Interval with Cardiac Nerve Stimulation.

Control and experimental H-V intervals for each nerve stimulated, before and after drug administration, are tabulated in Table 3. No significant changes were found for any of the perturbations.

### C. Changes in A-H Interval with Cardiac Nerve Stimulation.

Table 4 indicates the number of animals that responded to stimulation of a given cardiac nerve with an increase (I), decrease (D) or no change (N) in A-H interval before and after administration of the blocking agents. Utilizing this information the cardiac nerves were divided into three groups: sympathetic, parasympathetic, and mixed nerves.

The sympathetic nerves included the left ansae subclavia, ventro-lateral cardiac nerve, right ansae subclavia and right stellate cardiac nerves. All of these nerves either decreased or did not change the A-H interval before atropine or propranolol were administered. In addition, no parasympathetic effects of nerve stimulation were unmasked following propranolol. The decreases in A-H interval following propranolol were all minor (2-5 msec) and were presumably due to inadequate beta blockade. The innominate cardiac nerve also seems to be a predominately sympathetic nerve when it has an affect. However, one nerve of the eight tested did produce an increase in A-H interval when it was stimulated following propranolol. Thus, the innominate cardiac nerve might be considered a mixed nerve in its effects on atrioventricular conduction.

The right thoracic vagus was the only nerve with entirely parasympathetic input to the atrioventricular junction. Only increases in A-H interval were demonstrated before and after propranolol and before

TABLE 3

## EFFECT OF INDIVIDUAL CARDIAC NERVE STIMULATION ON H-V INTERVAL

NERVE STIMULATED	ATROPINE*				PROPRANOLOL*			
	BEFORE		AFTER		BEFORE		AFTER	
	CONTROL	STIMULATED	CONTROL	STIMULATED	CONTROL	STIMULATED	CONTROL	STIMULATED
Left ansae subclavia	30.6 $\pm$ 2.8	30.6 $\pm$ 2.8	30.3 $\pm$ 2.9	30.3 $\pm$ 2.9	32.5 $\pm$ 1.7	32.1 $\pm$ 1.7	33.1 $\pm$ 1.9	32.8 $\pm$ 1.9
Innominate c.n.	30.3 $\pm$ 2.9	30.3 $\pm$ 2.9	30.6 $\pm$ 2.7	30.7 $\pm$ 2.8	31.9 $\pm$ 1.6	31.8 $\pm$ 1.6	32.5 $\pm$ 1.6	32.5 $\pm$ 1.6
Ventromedial c.n.	30.4 $\pm$ 2.9	30.6 $\pm$ 3.0	30.0 $\pm$ 2.6	27.1 $\pm$ 4.2	31.5 $\pm$ 1.5	31.8 $\pm$ 1.6	32.8 $\pm$ 1.7	29.6 $\pm$ 3.8
Ventrolateral c.n.	30.3 $\pm$ 2.9	30.6 $\pm$ 3.1	30.6 $\pm$ 2.7	30.9 $\pm$ 2.8	31.8 $\pm$ 1.3	31.8 $\pm$ 1.3	32.5 $\pm$ 1.6	32.1 $\pm$ 1.9
Left thoracic vagus	29.7 $\pm$ 3.0	30.0 $\pm$ 2.9	30.0 $\pm$ 2.7	30.6 $\pm$ 2.9	31.5 $\pm$ 1.5	30.6 $\pm$ 1.7	33.1 $\pm$ 1.9	32.8 $\pm$ 2.1
Right ansae subclavia	30.6 $\pm$ 3.3	30.6 $\pm$ 3.0	30.0 $\pm$ 2.9	30.0 $\pm$ 3.1	31.6 $\pm$ 1.6	31.3 $\pm$ 1.5	32.5 $\pm$ 1.6	32.5 $\pm$ 1.6
Right stellate c.n.	30.3 $\pm$ 2.9	30.3 $\pm$ 2.9	30.6 $\pm$ 2.6	30.6 $\pm$ 2.9	31.0 $\pm$ 1.4	31.0 $\pm$ 1.4	32.8 $\pm$ 1.5	32.5 $\pm$ 1.6
Right recurrent c.n.	30.3 $\pm$ 2.9	30.0 $\pm$ 2.8	30.6 $\pm$ 2.9	30.6 $\pm$ 2.9	30.9 $\pm$ 1.4	30.9 $\pm$ 1.4	33.0 $\pm$ 1.6	33.0 $\pm$ 1.6
Craniovagal c.n.	30.3 $\pm$ 2.9	30.0 $\pm$ 2.8	30.6 $\pm$ 2.9	30.6 $\pm$ 2.9	30.9 $\pm$ 1.4	31.3 $\pm$ 1.5	32.5 $\pm$ 1.6	32.5 $\pm$ 1.6
Caudovagal c.n.	30.9 $\pm$ 3.3	30.3 $\pm$ 2.9	30.3 $\pm$ 2.8	30.6 $\pm$ 3.1	30.6 $\pm$ 1.4	30.6 $\pm$ 1.4	32.5 $\pm$ 1.6	32.5 $\pm$ 1.6
Right thoracic vagus	30.3 $\pm$ 2.9	30.9 $\pm$ 1.4	30.6 $\pm$ 2.6	30.6 $\pm$ 2.9	30.9 $\pm$ 1.4	31.3 $\pm$ 1.5	32.5 $\pm$ 1.6	32.5 $\pm$ 1.6

\*Values indicated are the mean  $\pm$  standard error of the mean of the H-V interval (msec). c.n.=cardiac nerve.

TABLE 4

## EFFECT OF INDIVIDUAL CARDIAC NERVE STIMULATION ON A-H INTERVAL

NERVE STIMULATED	ATROPINE*					PROPRANOLOL*					
	BEFORE			AFTER		BEFORE			AFTER		
	I	D	N	D	N	I	D	N	I	D	N
Left ansae subclavia	-	8	-	8	-	-	8	-	-	4	4
Innominate cardiac nerve	-	5	3	5	3	-	2	6	1		7
Ventromedial cardiac nerve	2	5	1	7	1	2	2	4	4		4
Ventrolateral cardiac nerve	-	7	1	6	2	-	8	-	-	2	6
Left thoracic vagus	8	-	-	3	5	8	-	-	8		-
Right ansae subclavia	-	8	-	7	1	-	8	-	-	1	7
Right stellate cardiac nerve	-	4	4	3	5	-	5	3	-		8
Right recurrent cardiac nerve	3	4	1	7	1	5	3	-	6		2
Craniovagal cardiac nerve	5	2	1	7	1	8	-	-	7		1
Caudovagal cardiac nerve	7	1	-	6	2	7	-	1	7		1
Right thoracic vagus	8		-	-	8	8	-	-	8		-

\*Number of animals exhibiting the indicated response out of a total of 8. I=Increase in A-H interval; D=Decrease in A-H interval; N=No change in A-H interval.

atropine. Following atropine all responses were eliminated.

The remaining cardiac nerves, the left thoracic vagus, the ventromedial cardiac nerve, the craniovagal and caudovagal cardiac nerves, send both sympathetic and parasympathetic input, in various ratios, to the atrioventricular junction. For example, the left thoracic vagus was predominately parasympathetic but three of eight nerves contained sympathetic components as well.

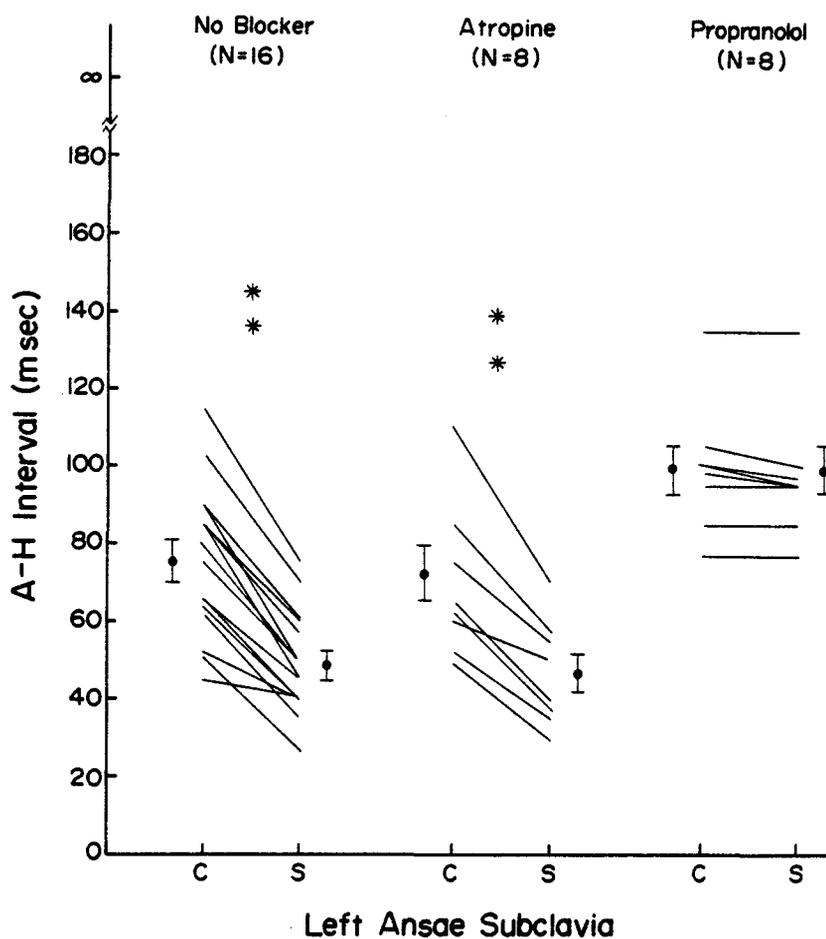
Thus, all cardiac nerves have potential influence over atrioventricular conduction although the magnitude of such effects has not yet been described.

Figure 6 illustrates the changes in A-H interval induced by stimulation of the left ansae subclavia. Each line represents the results of nerve stimulation in a single experiment. The mean  $\pm$  the standard error of the mean are also shown for each set of data. Before blocking agents were administered left ansae subclavia stimulation evoked a significant decrease in A-H interval from  $75.7 \pm 4.9$  msec to  $48.8 \pm 3.2$  msec, a change of  $35.2 \pm 2.6\%$ . Figure 7 shows the results of left ansae subclavia stimulation under these conditions in a single animal (panel A). The upper panel is just prior to left ansae stimulation. The traces are the electrograms from the left atrium, His bundle catheter, and left ventricular base. The A-H and H-V intervals were measured from the His bundle trace as described above and in this animal were 90 and 35 msec, respectively. The lower panel follows 5 seconds of left ansae subclavia stimulation. The A-H interval shortened to 62.5 msec, a change of 27.5 msec or 31%. The H-V interval remained constant at 35 msec.

Following atropine a similar decrease in A-H interval, from

FIGURE 6

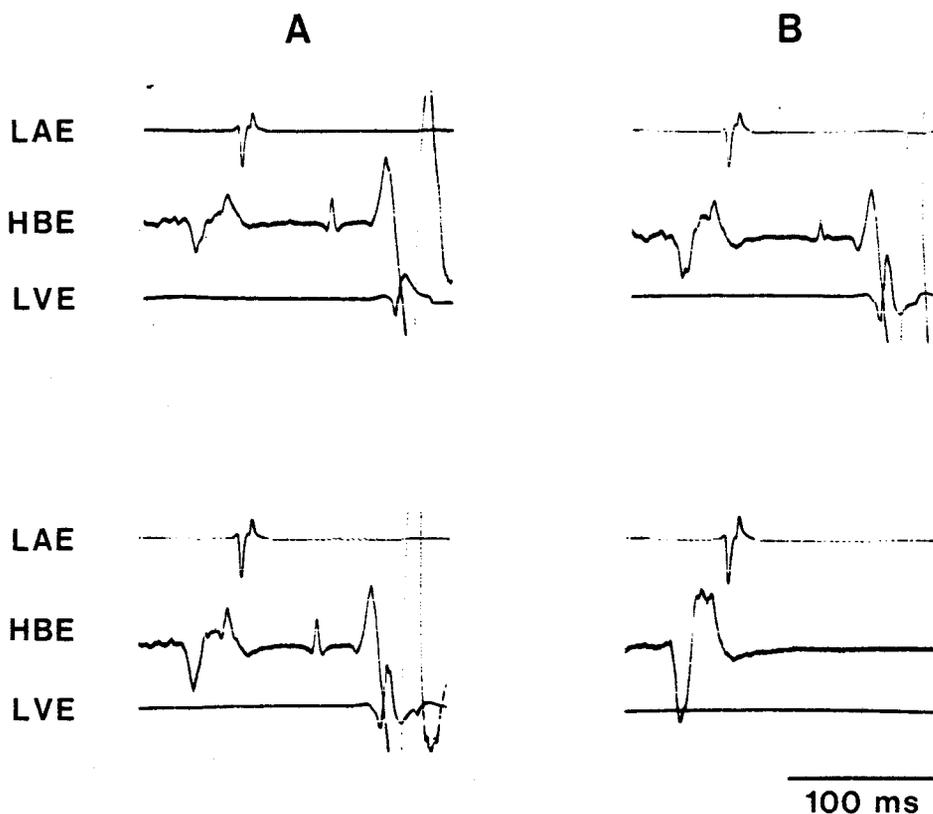
## EFFECT OF LEFT ANSAE SUBCLAVIA STIMULATION ON A-H INTERVAL



A-H interval prior to (C) and during (S) left ansae subclavia stimulation before blocking agents (no blocker), and after either cholinergic (atropine) or beta-adrenergic (propranolol) blockade. Lines connect pre-stimulation and stimulation responses in each dog examined.  $\bar{I}$  = mean  $\pm$  standard error of the mean;  $\infty$  = A-V block after 5 seconds of stimulation; \* =  $p < .05$ ; \*\* =  $p < .001$ .

FIGURE 7

EFFECT OF LEFT ANSAE SUBCLAVIA AND LEFT  
THORACIC VAGUS STIMULATION ON A-V CONDUCTION



Effects of left ansae subclavia (panel A) and left thoracic vagus (panel B) stimulation on atrioventricular conduction are shown. The upper traces in each panel are the control traces while the lower traces in each panel follow 5 seconds of the indicated nerve stimulation. Electrograms were recorded from the left atrium (LAE), His bundle catheter (HBE) and left ventricular base (LVE).

$72.7 \pm 7.5$  to  $46.9 \pm 4.8$  msec, was observed. This change was also significant. Propranolol, on the other hand, eliminated the response to left ansae subclavia stimulation. As shown in figure 6, the decreases in A-H interval seen in four animals following propranolol were minor. These results confirm the sympathetic nature of the left ansae subclavian distribution to the atrioventricular junctional region.

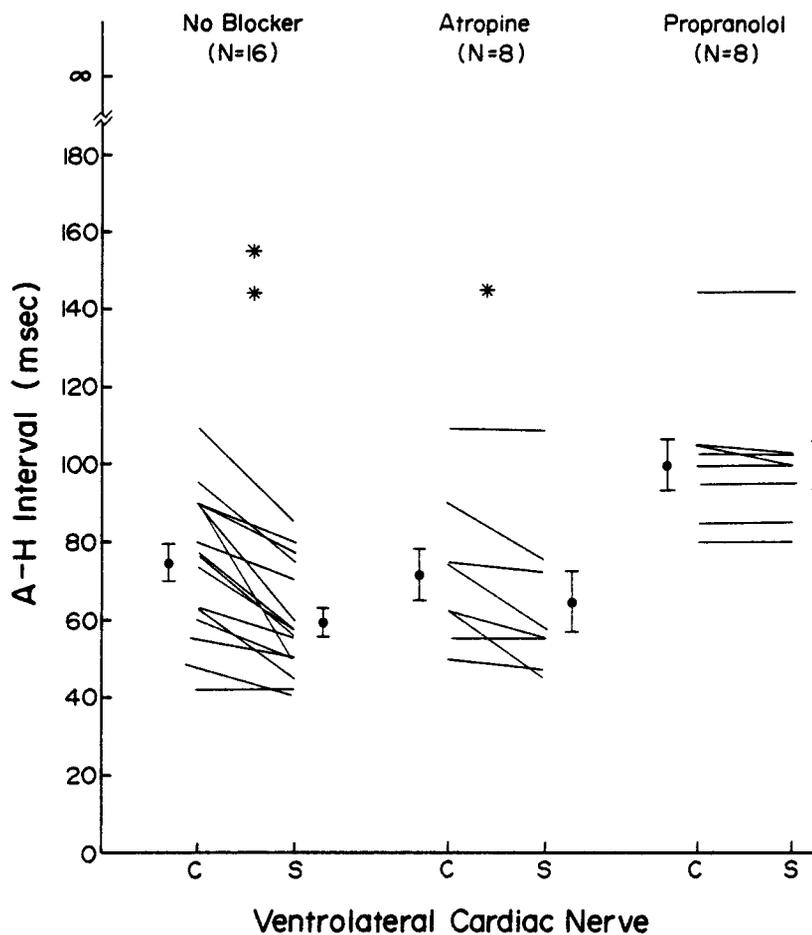
Similar to left ansae subclavia stimulation, stimulation of the ventrolateral cardiac nerve produced significant decreases in A-H interval before blocking agents and following atropine (figure 8). These changes were eliminated by propranolol. However, the magnitude of the changes were smaller for ventrolateral cardiac nerve stimulation than for left ansae subclavia stimulation. Before blocking agents stimulation of the nerve consistently decreased A-H interval  $19.2 \pm 2.6\%$ , from  $75.6 \pm 4.8$  to  $60.2 \pm 3.5$  msec. Following atropine, the A-H interval was decreased from  $72.5 \pm 7.0$  msec to  $65.0 \pm 7.6$  msec by ventrolateral cardiac nerve stimulation.

Stimulation of the right ansae subclavia (figure 9) also produced a significant decrease in A-H interval before drug administration ( $72.5 \pm 4.6$  to  $50.1 \pm 3.7$  msec). This decrease was  $30.9 \pm 2.8\%$  compared to the  $35.2\%$  change produced by left ansae subclavia stimulation. Following atropine A-H interval decreased from  $69.1 \pm 5.8$  to  $51.3 \pm 3.5$  msec. These effects were eliminated by propranolol.

Although the right stellate cardiac nerve conducts sympathetic activity to the atrioventricular junctional region it does not produce a large effect. As presented in figure 10 the right stellate cardiac nerve produced a significant decrease in A-H interval before blockers.

FIGURE 8

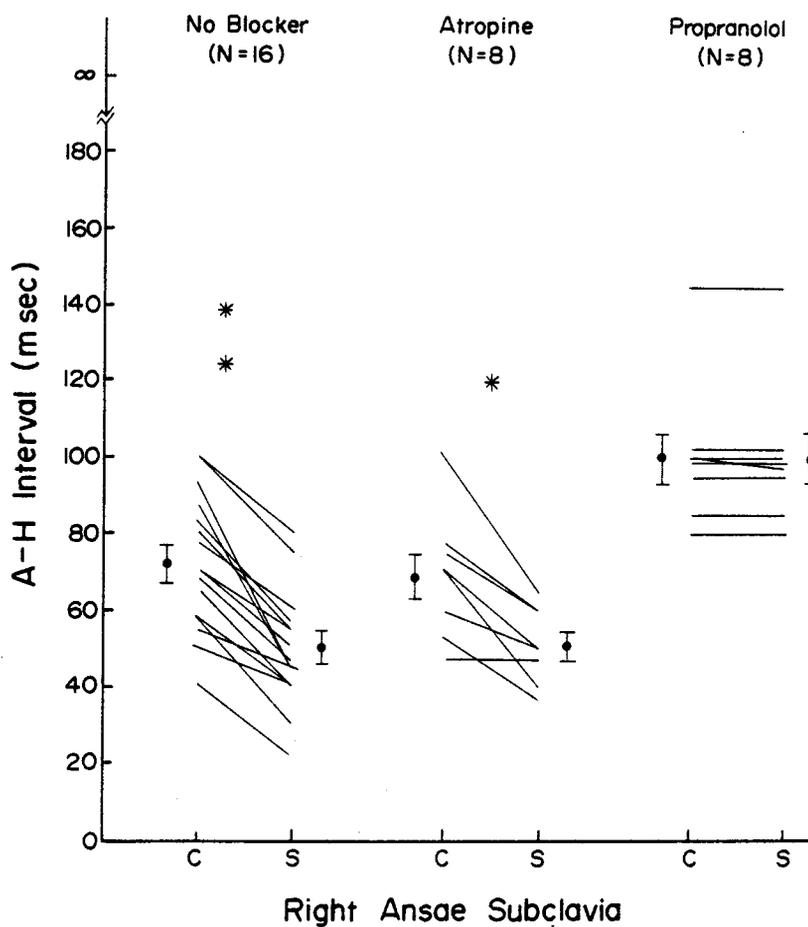
EFFECT OF VENTROLATERAL CARDIAC NERVE STIMULATION ON A-H INTERVAL



A-H interval prior to (C) and during (S) stimulation of the ventrolateral cardiac nerve under the three conditions of 1) before blocking agents (no blockers), 2) after atropine, and 3) after propranolol. Lines connect control and stimulation values for each dog examined. Symbols as in figure 6.

FIGURE 9

## EFFECT OF RIGHT ANSAE SUBCLAVIA STIMULATION ON A-H INTERVAL



A-H interval prior to (C) and during (S) right ansae subclavia stimulation before blocking agents and after atropine or propranolol. Lines connect pre-stimulation and stimulation A-H intervals for each nerve stimulated. Symbols as in figure 6.

However, this was only a  $9.9 \pm 2.9\%$  change, decreasing from  $72.6 \pm 4.7$  to  $67.3 \pm 5.1$  msec. Following blocking agents no significant effect was present. Thus the right stellate cardiac nerve supplies sympathetic fibers to the atrioventricular junction in some cases but these fibers only produce minor affects on conduction.

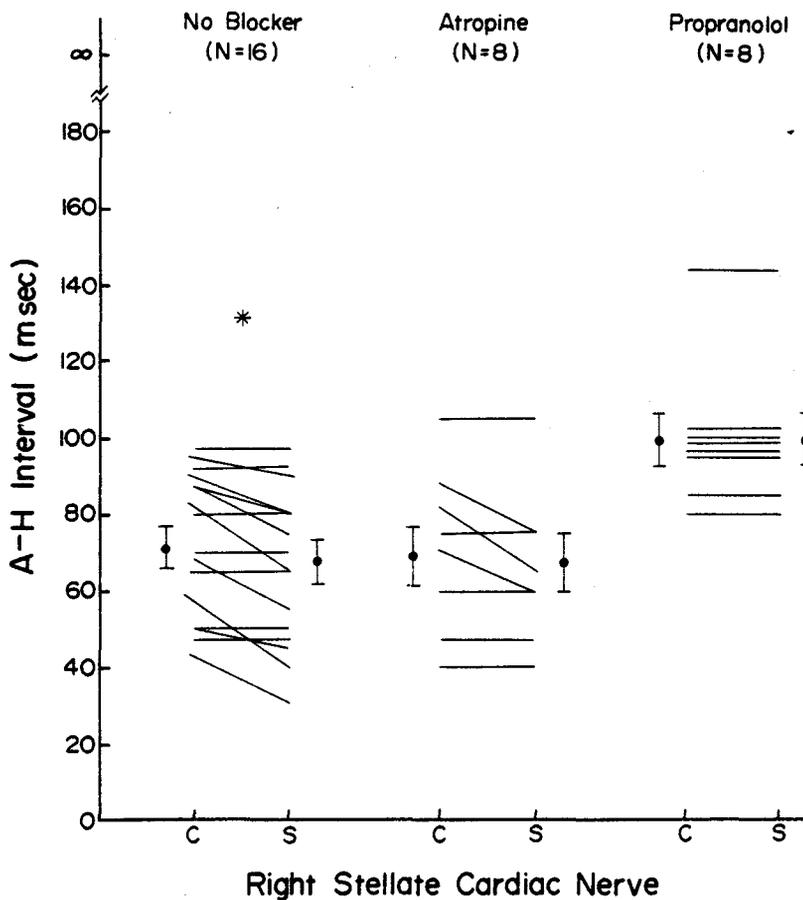
Following a pattern similar to that of the right stellate cardiac nerve, innominate cardiac nerve stimulation (figure 11) produced a significant, although small, decrease in A-H interval before blockers ( $76.1 \pm 4.9$  to  $71.5 \pm 5.1$  msec, or  $7.2 \pm 2.5\%$ ) but no change following atropine or propranolol ( $69.1 \pm 6.6$  to  $63.1 \pm 5.8$  msec and  $99.6 \pm 6.5$  to  $101.8 \pm 8.5$  msec, respectively).

The effect of left thoracic vagus stimulation under the same three conditions (before blockers, after atropine and after propranolol) are shown in figure 12. Once again each line represents the results of nerve stimulation in a single experiment. An A-H interval of  $\infty$  indicates the occurrence of complete atrioventricular block when the oscilloscope trace was taken after 5 seconds of nerve stimulation. An example of such a trace is shown in figure 7 (panel B). The upper panel is just prior to stimulation of the left thoracic vagus while the lower panel follows 5 seconds of stimulation. The presence of A-V block, as evidenced by atrial depolarization without ventricular depolarization, was verified in each case by the lead II EKG recording.

After 5 seconds of left thoracic vagus stimulation 11 dogs were in A-V block and the remaining 5 animals demonstrated a mean increase in A-H interval of 41.5 msec from a control value of  $75.3 \pm 4.5$  msec for the 16 dogs. Stimulation of the left thoracic vagus after beta blockade

FIGURE 10

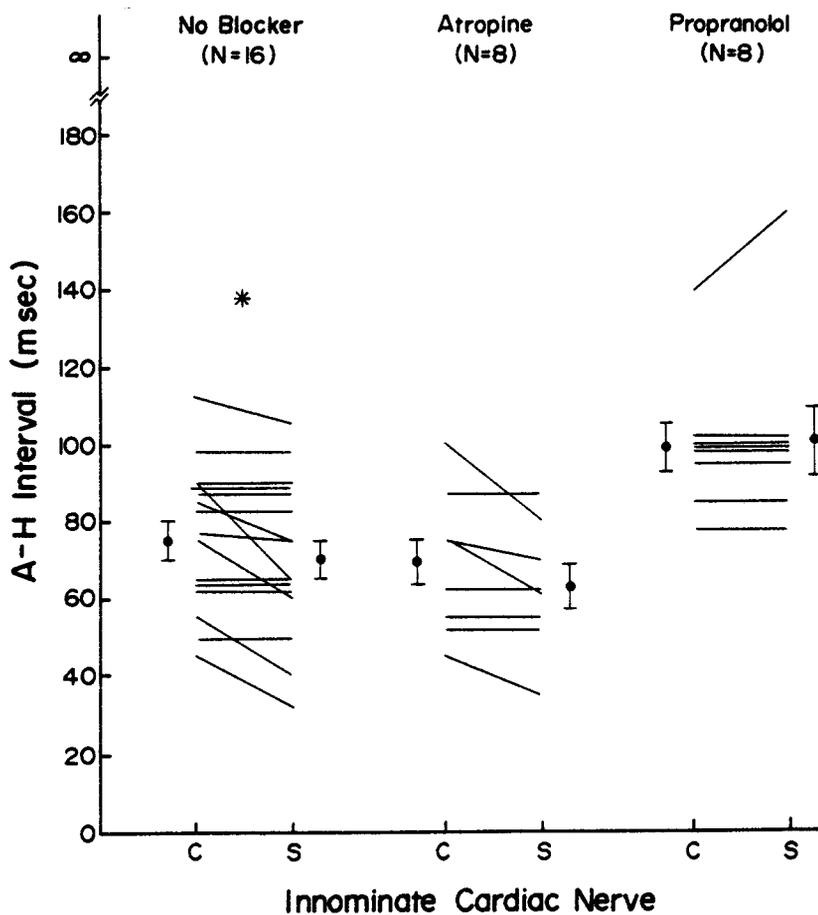
## EFFECT OF RIGHT STELLATE CARDIAC NERVE STIMULATION ON A-H INTERVAL



A-H interval before (C) and during (S) right stellate cardiac nerve stimulation before blocking agents (no blockers) and after either cholinergic (atropine) or beta adrenergic (propranolol) blockade. Symbols as in figure 6.

FIGURE 11

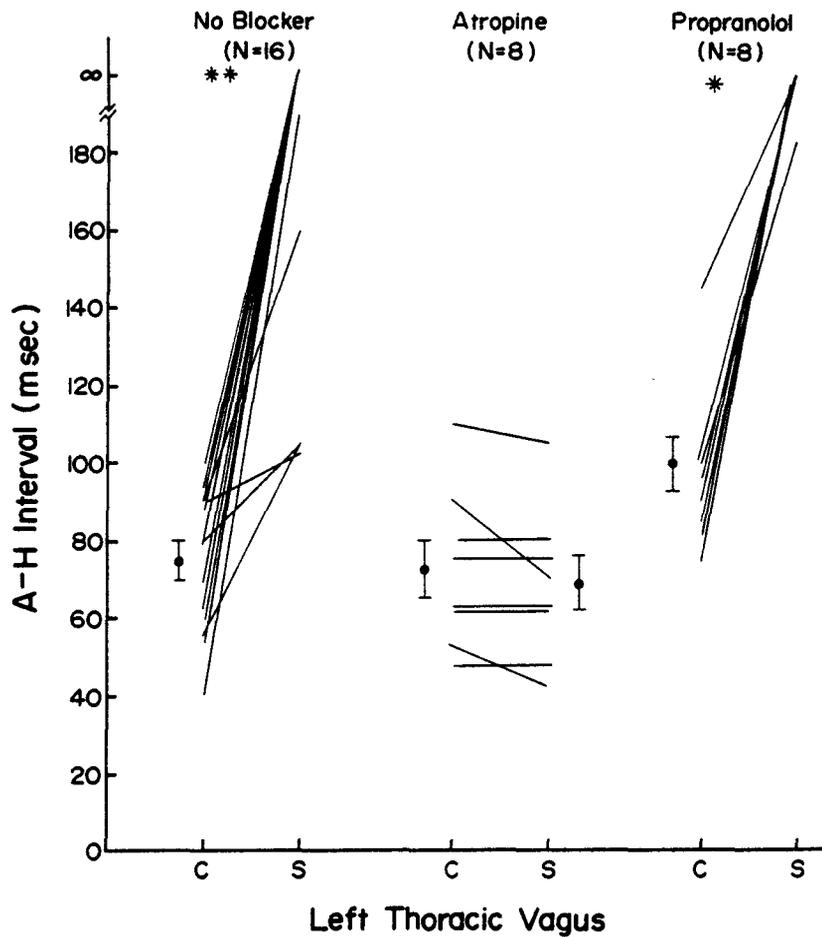
EFFECT OF INNOMINATE CARDIAC NERVE STIMULATION ON A-H INTERVAL



A-H interval before (C) and during (S) innominate cardiac nerve stimulation before blocking agents and following atropine or propranolol. Control and stimulation values are connected by a line for each nerve stimulated. Symbols as in figure 6.

FIGURE 12

## EFFECT OF LEFT THORACIC VAGUS STIMULATION ON A-H INTERVAL



A-H interval prior to (C) and during (S) left thoracic vagus stimulation before blocking agents (no blocker) and after either cholinergic (atropine) or beta adrenergic (propranolol) blockade. Lines connect control and stimulation responses in each dog examined. Symbols as in figure 6.

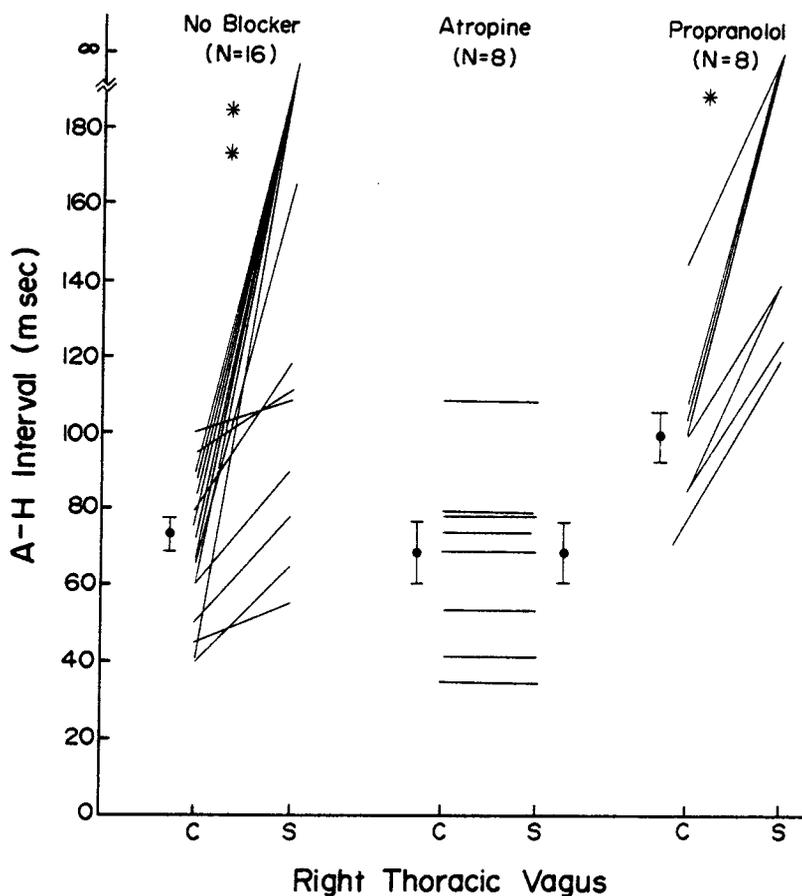
produced A-V block in 7 of 8 dogs. These changes produced by nerve stimulation were significant but were abolished by atropine. Overall left thoracic vagus stimulation following atropine changed the A-H interval from  $72.5 \pm 7.3$  msec to  $68.4 \pm 7.0$  msec. In the three dogs with an unmasked sympathetic component the average change was only 10.0 msec.

Prior to the administration of a blocking agent right thoracic vagus stimulation caused A-V block in 8 hearts and a mean increase in A-H interval of 31.9 msec in the remaining 8 hearts (figure 13). The control A-H interval was  $73.9 \pm 4.9$  msec. Atropine totally eliminated this response, and no sympathetic responses were seen. Thus, A-H interval was constant at  $70.3 \pm 7.7$  msec. Following propranolol the control A-H interval increased to  $100.8 \pm 7.0$  and stimulation produced A-V block in 5 dogs and a mean increase of 42.5 msec in the three remaining dogs. The changes observed before blocking agents and following propranolol were both significant.

The results of stimulation of the craniovagal (figure 14) and caudovagal (figure 15) cardiac nerves showed marked similarities. Prior to autonomic blockade both nerves produced a significant prolongation of A-H interval and thus may be considered predominately parasympathetic nerves. Craniovagal cardiac nerve stimulation elicited A-V block in 7 animals, the remaining 9 nerves producing a mean increase in A-H interval of 14.5 msec. Caudovagal cardiac nerve stimulation produced A-V block in 8 animals prior to blockade. The mean response to stimulation of the remaining nerves was an increase in A-H interval of 26.2 msec. The prolongation effect of stimulation of these two nerves was not abolished

FIGURE 13

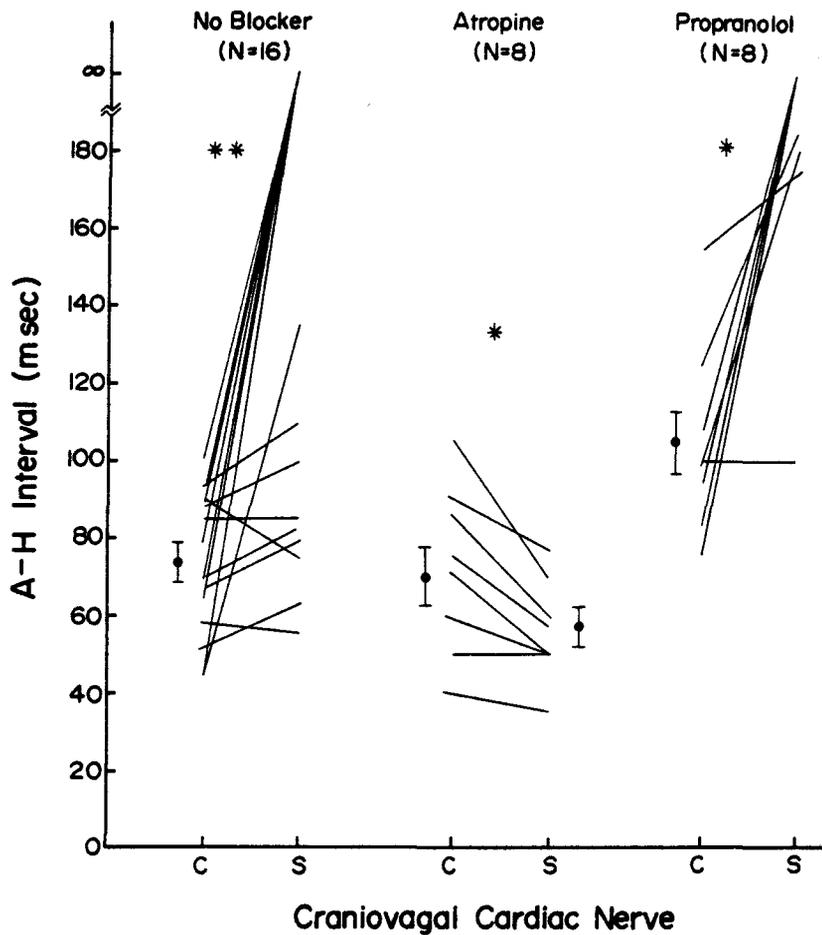
EFFECT OF RIGHT THORACIC VAGUS STIMULATION ON A-H INTERVAL



A-H interval prior to (C) and during (S) stimulation of the right thoracic vagus before (no blockers) and after either cholinergic (atropine) or beta adrenergic (propranolol) blockade. Lines connect the control and stimulation values for each experiment. Symbols as in figure 6.

FIGURE 14

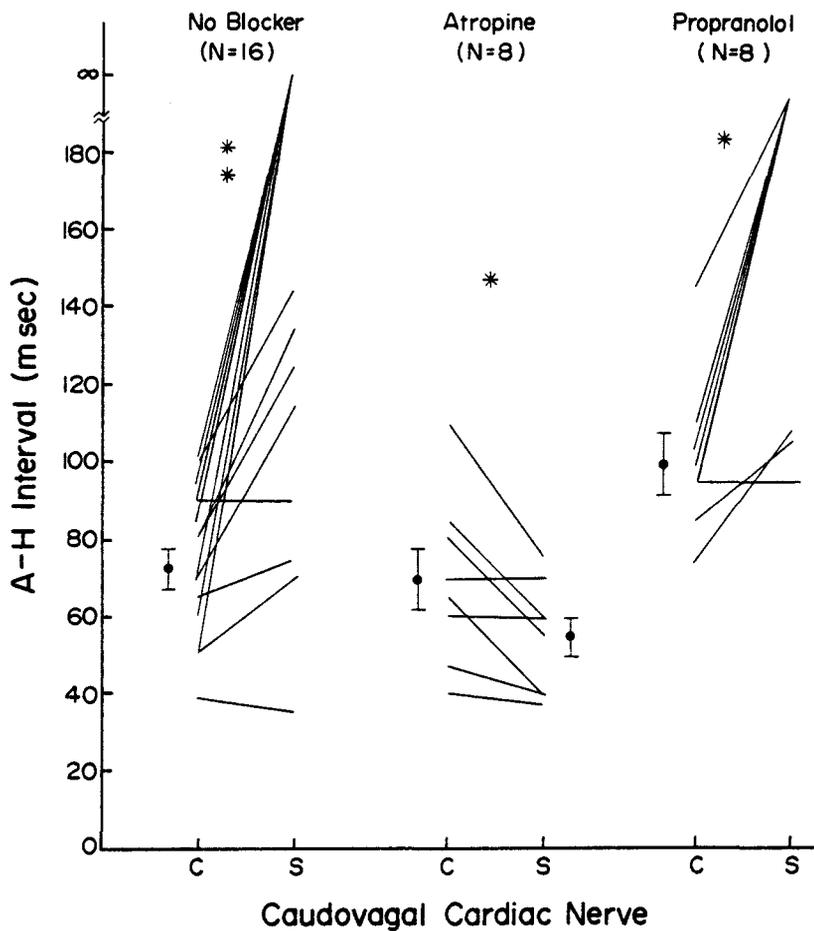
EFFECT OF CRANIOVAGAL CARDIAC NERVE STIMULATION ON A-H INTERVAL



A-H interval prior to (C) and during (S) stimulation of the craniovagal cardiac nerve before blocking agents (no blockers) and following administration of atropine or propranolol. Lines connect the control and stimulation values for each nerve tested. Symbols as in figure 6.

FIGURE 15

## EFFECT OF CAUDO-VAGAL CARDIAC NERVE STIMULATION ON A-H INTERVAL



A-H intervals prior to (C) and during (S) caudovagal cardiac nerve stimulation before blocking agents (no blockers) and following either cholinergic (atropine) or adrenergic (propranolol) blockade. Control and stimulation values for each experiment are connected by a line. Symbols as in figure 6.

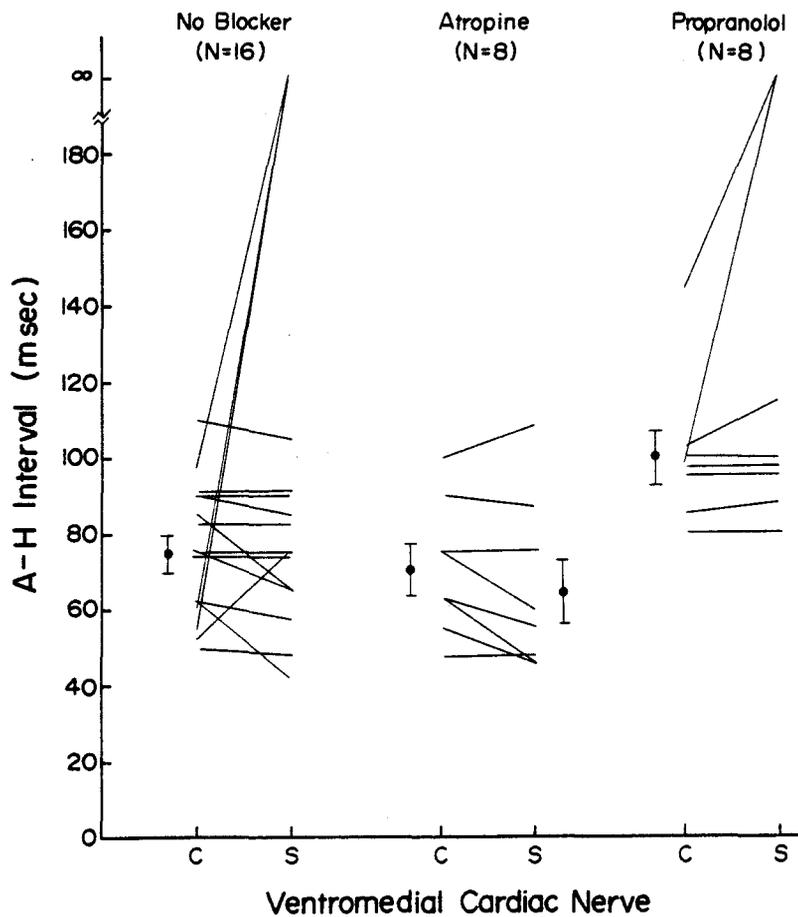
by adrenergic blockade, but cholinergic blockade unmasked a significant affect of craniovagal and caudovagal cardiac nerve stimulation on atrioventricular conduction. Craniovagal cardiac nerve stimulation decreased A-H interval from  $71.3 \pm 7.7$  msec to  $57.5 \pm 4.5$  msec, while caudovagal cardiac nerve stimulation decreased this interval from  $70.9 \pm 8.1$  to  $55.3 \pm 5.2$  msec.

The ventromedial cardiac nerve, although containing both parasympathetic and sympathetic components as shown in Table 4, failed to produce a significant change in atrioventricular conduction. A-V block occurred with stimulation of 3 ventromedial cardiac nerves prior to blockade, 5 did not change conduction and the remaining 8 produced variable effects (figure 16). Following atropine A-H interval decreased from  $70.9 \pm 6.3$  to  $65.3 \pm 8.1$  msec with nerve stimulation. Following propranolol, two nerves caused A-V block, 2 others caused minor conduction slowing, and the remaining 4 nerves produced no effect when stimulated.

The right recurrent cardiac nerve is unique. As shown in figure 17 it is capable of exerting both significant parasympathetic and significant sympathetic affects on atrioventricular conduction while neither system predominates. Before blocking agents were given right recurrent cardiac nerve stimulation changed A-H interval from  $73.6 \pm 4.4$  msec to  $78.7 \pm 6.9$  msec. Although this change was not statistically significant, only one nerve failed to elicit a response when stimulated. The mean incese in A-H interval produced by the 8 predominately parasympathetic nerves was 18.8 msec, while the mean decrease in A-H interval produced by the 8 predominately sympathetic nerves was 10.1 msec. Atropine revealed the capability of right recurrent cardiac nerve

FIGURE 16

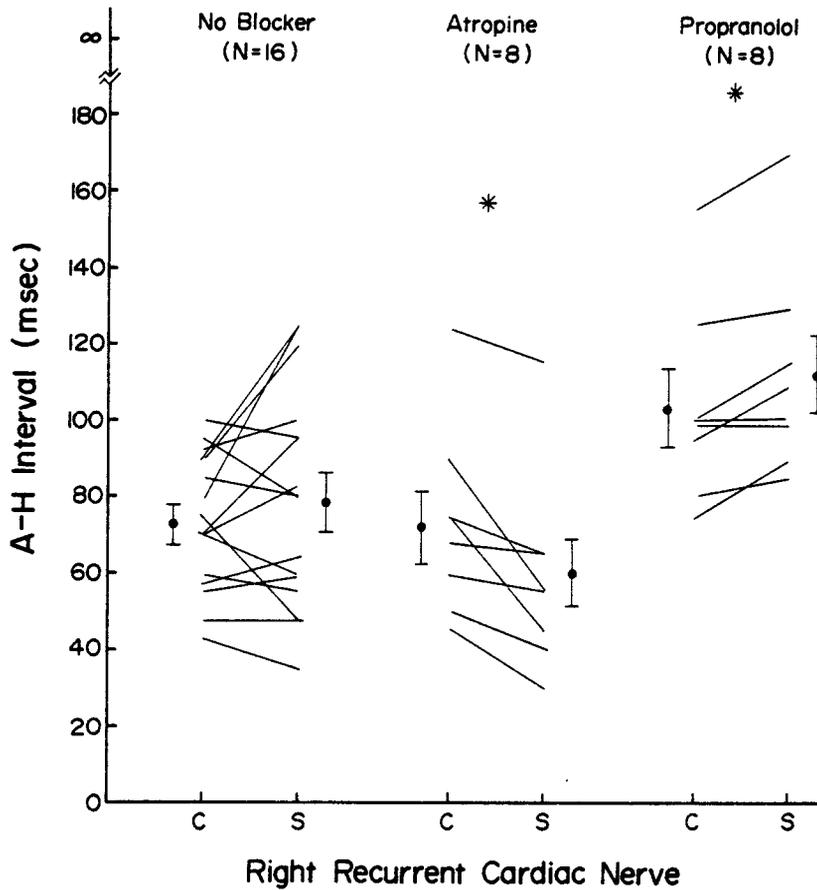
## EFFECT OF VENTROMEDIAL CARDIAC NERVE STIMULATION ON A-H INTERVAL



A-H interval prior to (C) and during (S) stimulation of the ventromedial cardiac nerve before blockers and after either atropine or propranolol. Lines connect pre-stimulation and stimulation responses in a single animal. Symbols as in figure 6.

FIGURE 17

EFFECT OF RIGHT RECURRENT CARDIAC NERVE STIMULATION ON A-H INTERVAL



A-H interval before (C) and during (S) right recurrent cardiac nerve stimulation, before (no blockers) and after either atropine or propranolol. Lines connect pre-stimulation and stimulation responses in a single experiment. Symbols as in figure 6.

stimulation to exert a significant sympathetic affect on atrioventricular conduction by reducing the A-H interval to  $60.3 \pm 9.1$  msec from  $73.1 \pm 8.7$  msec. In addition, stimulation of this nerve produced significant parasympathetic affects on atrioventricular conduction following propranolol. Here stimulation changed the A-H interval from  $103.8 \pm 9.1$  msec to  $112.5 \pm 9.6$  msec.

## DISCUSSION

### A. Normal A-H and H-V Intervals.

Initial interest in the range of normal values for A-H and H-V intervals was related to their use in clinical diagnosis of A-V conduction disorders. Thus, many values are supplied in the clinical literature. Most interest focused on the H-V interval because placement of the His bundle catheter may result in the recording of proximal bundle branch electrical activity rather than His bundle activity. Thus, invalid and abnormally short H-V intervals were found to be skewing the range for normal conduction measurements. In reaction to this problem, Narula (22) suggested that the upper and lower limits of a normal H-V interval should be set at 45 and 35 msec, respectively, based upon measurements which had been validated through the use of His bundle pacing. In the present study many of the pre-stimulation measurements of H-V interval were below the normal range suggested by Narula. However, this may be related to a species difference, as well as the use of anesthesia, artificial ventilation and an open chest preparation, as Narula's H-V interval limits were based upon measurements in unanesthetized human patients.

A study by Scherlag et al. (35), in 20 dogs anesthetized with sodium pentobarbital, reported normal H-V intervals of  $33 \pm 9$  msec (mean  $\pm$  SD). Repositioning of the His bundle catheter under fluoroscopy permitted Scherlag to record potentials from the proximal left bundle branch (PLB). This resulted in the measurement of a significantly ( $p < .01$ ) shorter interval, the PLB-V interval ( $21 \pm 1$  msec, mean  $\pm$  SD).

Control H-V intervals in the present study ( $30.7 \pm 1.5$  msec, mean  $\pm$  SE, for the 16 dogs) are in good agreement with those reported by Scherlag et al. (35). All but one of these dogs had an H-V interval in the range of 25-45 msec under control conditions. In the last animal (chloralose anesthetized) the H-V interval was 22.5 msec. As this value was close to the range Scherlag et al. (35) reported for a PLB-V interval, it is possible that the electrical activity recorded from this dog originated in the region of the left bundle branch rather than the His bundle. The shorter H-V interval could also have been related to a difference in anesthesia. However, this was less likely as the other chloralose anesthetized dogs were well within the normal range, at 27.5, 27.5 and 42.5 msec.

Although normal values for A-H intervals have been reported in the clinical literature the range is very broad due to the modulation of this interval by the autonomic nervous system. Narula et al. (22) reported a range of A-H intervals from 50-120 msec in patients with a normal P-R interval. The range of pre-stimulation values reported in the present study was similar to this range.

#### B. Comparison to Similar Studies.

A comparison of Tables 1 and 4 (before blockers) demonstrates the qualitative similarities between the results of the present study and the results of Geis et al. (7). In the Geis study, as in this study, the left and right ansae subclavia, the ventrolateral cardiac nerve and the innominate cardiac nerve were found to have sympathetic effects, the left and right thoracic vagi were found to produce predominately parasympathetic effects, and the right recurrent, craniovagal and caudovagal cardiac nerves

were found to produce both types of responses. The only qualitative difference between the Geis study and the present work was found in the effects of ventromedial cardiac nerve stimulation on atrioventricular conduction or rate. Geis et al. (7) elicited only sympathetic responses during ventromedial cardiac nerve stimulation, while 4 out of the 16 dogs demonstrated parasympathetic effects in the present study.

Quantitatively, more differences are evident. In the present study, stimulation of an individual cardiac nerve elicited some sort of measurable change in atrioventricular conduction in most instances. Even the innominate cardiac nerve had some effect on atrioventricular conduction in 7 of the 16 dogs. Geis et al. however, found few cardiac nerves which, when stimulated, elicited a response in atrioventricular rate in the majority of dogs. This difference between the two studies was especially prominent for the nerves of the right side. For example, right recurrent cardiac nerve stimulation had an effect in only 3 out of 11 dogs in the Geis study, while 15 out of 16 dogs demonstrated altered A-H intervals in the present study. These differences further support the suggestion made above that nerve fibers to the A-V junctional area, particularly those from the right side, may have been cut while eliminating the sinoatrial nodal innervation.

A comparison of the results of this study to those of Fishman et al. (4,5) also show similarities and differences. Fishman et al. demonstrated that the ventrolateral cardiac nerve was a predominately sympathetic cardiac nerve with effects on atrioventricular conduction of the same order of magnitude as those of the left ansae subclavia. These results were similar to those reported in the present study. However, the

results of right recurrent cardiac nerve stimulation presented here are not in agreement with the results of Fishman (4) who showed that stimulation of this nerve produced significant ( $p < .01$ ) sympathetic effects on the functional and effective refractory periods. In this study a significant sympathetic component of the right recurrent cardiac nerve to the A-V junction was demonstrated only after the administration of atropine. The reasons for this discrepancy are unclear. Although different techniques were used to measure the effects of nerve stimulation on atrioventricular conduction (conduction time vs. refractory periods), it seemed unlikely that this could be the cause of the difference in the results. Another more likely explanation was based on anatomical variability in the nerve locations on the right side. It is possible that the anatomical selection of the nerve was different between the two studies. A final possibility was that one, or both, of the studies did not represent a true random sample from the population. For example, if the majority of the animal population consisted of dogs with right recurrent cardiac nerves having predominately sympathetic components, but within this population there was a minority of dogs with predominately parasympathetic components, these two studies would only differ in the number of less frequent, parasympathetic nerves included in the study.

#### C. Structure-Function Relationships of the Cardiac Nerves.

Descriptions of the structure-function relationships of the canine cardiac nerves began with the work of Mizeres (18). He not only provided an accurate anatomical description, but sought to discover the pathways by which positive and negative chronotropic responses were produced. Randall and co-workers (3,24,27,29) continued along these lines of

inquiry with studies that examined the differential endocardial and epicardial inotropic responses produced by stimulation of the individual cardiac nerves. Armour (2,3) added histological and functional data concerning the afferents contained in the individual cardiac nerves to the volume of literature. The present study is the first systematic study of the dromotropic effects of the cardiac nerves upon the atrio-ventricular junctional region. The functional information gained can be related to the anatomical projection of the cardiac nerves. This information also adds to understanding of the role of each individual cardiac nerve in controlling cardiac function.

In the dog, the vagi descend from the nodose ganglia and intermingle with sympathetic fibers coursing from the caudal cervical ganglia and the superior cervical ganglion. This anatomical arrangement accounts for the combined sympathetic and parasympathetic cardiac responses to cervical vagal stimulation (26,28). The caudal cervical ganglion receives its sympathetic fibers from the stellate ganglion via the ansae subclavia and generally is intimately connected to the vagus in the dog. Because of this relationship, electrical stimulation of most of the individual cardiac nerves distal to the location of the caudal cervical ganglion elicits mixed sympathetic and parasympathetic responses.

The ventrolateral cardiac nerve is the largest of the sympathetic nerves on the left side. It arises from the lateral, inferior pole of the caudal cervical ganglion, and descends lateral to the vagus while exchanging fibers with it. Studies by Randall and co-workers (24,27,29) have shown that stimulation of this nerve elicits the most widespread increases in contractile force of any of the cardiac nerves. Virtually

all epicardial surfaces of the left ventricle and the anterior surface of the right ventricle were affected with primary alterations on the posterior surfaces and the left atrium. Minor changes in contractility occurred over the ventral left ventricular surfaces, the right ventricle, and the right atrium (24). Although the ventrolateral cardiac nerve was distributed primarily to the epicardial surfaces of the left ventricle, it supplied both the right and left ventricular endocardial surfaces producing large contractile force increases in all papillary muscles and the lower portions of the interventricular septum. Smaller changes were observed in the upper portions of the interventricular septum (3). Although studies by Kralios et al. (14) demonstrated similar regional changes in refractory period on the epicardial surface, they did not find any changes in refractory period in the interventricular septum.

The magnitude of the inotropic changes seen with ventrolateral cardiac nerve stimulation approached those observed with left ansae subclavia stimulation. Thus, it can be inferred that the ventrolateral cardiac nerve carries a substantial portion of the left ansae subclavial, and thus the left sympathetic, fibers to the myocardium. The present study supports this inference. In many cases the sum of the decreases in A-H interval elicited by ventrolateral, ventromedial and innominate cardiac nerve stimulation was equal to the decrease in A-H interval elicited by left ansae subclavia stimulation. However, as the ventrolateral cardiac nerve produced major changes in A-H interval while the other two nerves produced only minor changes, it must be concluded that a major portion of the left sympathetics travel to the atrioventricular junction via the ventrolateral cardiac nerve. Ventrolateral cardiac nerve stimulation

produced a  $19.2 \pm 2.6\%$  decrease in A-H interval compared to the  $35.2 \pm 2.6\%$  decrease elicited by left ansae subclavia stimulation.

Geesbrecht et al. (6) showed that stimulation of the ventrolateral cardiac nerve produced little change in sinus rate. Rather, a pacemaker shift from the sinoatrial nodal region to the coronary sinus or atrio-ventricular junctional region was elicited. In the present study, stimulation of the ventrolateral cardiac nerve for longer than 5-10 seconds produced a disruption of the pacing rhythm as the rate accelerated beyond the pacing rate of 200 beats per minute. When the stimulation and pacing were discontinued, the lead II EKG demonstrated a pattern typical of a junctional pacemaker (absence of a recognizable P wave). As the rate slowed, the P wave would return. This pattern of response was also observed during left ansae subclavia stimulation but never during stimulation of any of the remaining cardiac nerves.

Parasympathetic inotropic and chronotropic effects have not been reported during stimulation of the ventrolateral cardiac nerve. As shown in the present study, the ventrolateral cardiac nerve produces large decreases in A-H interval when stimulated. Following propranolol, no increases in A-H interval were observed indicating the absence of a functional parasympathetic component to the atrioventricular junction. Thus, although the anatomical source of the ventrolateral cardiac nerve does not exclude the possibility of the presence of parasympathetic fibers in this nerve, there is no functional evidence for their presence.

The innominate cardiac nerve is formed from filaments of the vagosympathetic trunk arising just rostral to the caudal cervical ganglion and from the caudal cervical ganglion itself. It courses along the

innominate artery medial to the thoracic vagus (3). Although the anatomical source of the innominate cardiac nerve would also suggest a complement of both sympathetic and parasympathetic fibers, few of the possible parasympathetic fibers contained in this nerve innervate the atrioventricular junction. Stimulation of this nerve decreased the A-H interval in 7 out of 16 animals, with the remaining 9 demonstrating no change. Following propranolol only 1 out of 8 dogs demonstrated an increase in A-H interval during innominate nerve stimulation.

Parasympathetic inotropic and chronotropic changes can be elicited by innominate nerve stimulation although these changes are primarily sympathetic in nature. Stimulation of this nerve produced distinct alterations in the force of contraction, particularly at the apical regions of both the right and left ventricles, and in the left ventricular papillary muscles. Only minor inotropic changes were elicited in the right ventricular conus, the dorsal and lateral surfaces of the left ventricle and the right ventricular papillary muscles. The innominate cardiac nerve rarely changed heart rate (3).

The remaining cardiac nerve on the left side, the ventromedial cardiac nerve, is made up of one or two branches arising from the medial left thoracic vagus, or directly from the caudal pole of the caudal cervical ganglion. This nerve courses just medial to the thoracic vagus and, occasionally, appears to lie within the same sheath as the vagus itself. The relationship between this nerve and the vagus plays a definite role in its functional effects on A-V conduction. Of the 5 nerves which were found to lie immediately adjacent to the thoracic vagus, 4 nerves produced increases in A-H interval when stimulated and the

fifth nerve elicited no change. None of the ventromedial cardiac nerves which were distinctly separate from the vagus increased the A-H interval. Overall the changes in atrioventricular conduction elicited by ventromedial cardiac nerve stimulation were small and in 5 of the 16 dogs stimulation had no effect on A-H interval. Interestingly, the animals which were unaffected by ventromedial cardiac nerve stimulation often responded to innominate stimulation (3 out of 5), and those dogs unaffected by innominate cardiac nerve stimulation responded to ventromedial cardiac nerve stimulation (7 out of 9). In 4 animals both nerves altered A-H interval, while in 2 dogs neither nerve changed this interval.

Randall et al. (29) showed that electrical excitation of the ventromedial cardiac nerve elicited marked changes in contractile force in the right ventricular conus with less augmentation in the sinus. A modest change also occurred in the apical lateral surfaces of the left ventricle. Unlike the ventrolateral cardiac nerve which increased inotropy in all papillary muscles and the innominate cardiac nerve which increased inotropy in the left ventricular papillary muscles, the ventromedial cardiac nerve had its predominate influence on the right ventricular papillary muscles. The ventromedial cardiac nerve occasionally produced parasympathetic changes in contractile force and in heart rate. The location of these nerves with respect to the vagus were not described however.

The right recurrent cardiac nerve also innervates the atrioventricular junctional region. This cardiac nerve arises from the right recurrent laryngeal nerve as it loops around the right subclavian artery and receives branches from the caudal cervical ganglion and from other

right cardiac nerves. As demonstrated in the present study, the right recurrent cardiac nerve carries sympathetic and parasympathetic fibers, each of which produce significant changes in A-H interval when stimulated after appropriate blocking agents. The right recurrent cardiac nerve also carries both sympathetic and parasympathetic influences of the autonomic nervous system to the sinoatrial node, and to the musculature as shown by Randall et al. (29). Following atropine positive inotropic changes induced by efferent stimulation of this nerve were found on most epicardial surfaces of the right ventricle with some augmentation in contractile force present as far distally as the apex of the left ventricle. Endocardially, stimulation of the right recurrent cardiac nerve produced widely distributed effects, changing contractile force in all of the papillary muscles. Kralios et al. (14) reported a more limited distribution of the right recurrent cardiac when they examined the responses to premature stimuli (refractory period determinations) during nerve stimulation. Intense changes were found in the inter-ventricular septum during recurrent cardiac nerve stimulation, while lesser responses were seen on the anterior surface of the left ventricle.

The craniovagal and caudovagal cardiac nerves each consist of several smaller nerves arising from the vagal trunk. The craniovagal cardiac nerve exits the vagus just inferior to the caudal cervical ganglion, while the caudovagal cardiac nerve arises more distally from the thoracic vagus. These nerves usually initiate negative chronotropic and inotropic responses and contain many afferent nerves from receptors located in the right heart (3). Following atropine, positive chronotropic and inotropic responses were elicited during nerve stimulation. The

craniovagagal cardiac nerve produced augmentation of contractile force in the right ventricle with relatively greater changes in the conal region. Only minor changes were seen in the left ventricle. The caudovagal cardiac nerve produced similar although less extensive, changes after atropine. Its effects were limited to the conal and sinus musculature of the right ventricle. In addition, this nerve produced only a minor acceleration in heart rate following atropine.

The final cardiac nerve to be discussed is the right stellate cardiac nerve. This nerve innervates the atrioventricular junction to only a small extent. The right stellate cardiac nerve is composed of numerous small filaments arising from the rostral pole of the stellate ganglion, the ventral ansa subclavia, or the inferior portion of the caudal cervical ganglion. It crosses the right thoracic vagus at the level of the caudovagal cardiac nerve. Fibers from the right stellate cardiac nerve may intermingle with those of the craniovagagal and caudovagal cardiac nerves and the right thoracic vagus (3). Stimulation of the right stellate cardiac nerve gives rise to a large acceleration in heart rate (sinus rhythm) with only modest positive inotropic changes in right atrial contractility. Thus this nerve has been described as a purely positive chronotropic nerve. Norris et al. (24) reports one case in which heart rate accelerated from 165 to 290 beats per minute. In the present study there was also a marked tendency for heart rate to exceed the pacing rate of 200 beats per minute when the nerve was stimulated for longer than 5-10 seconds. However, as noted, this nerve innervates the A-V junction to only a small extent. In the 9 dogs in which a response occurred the decrease in A-H interval was only 5-17.5 msec.

In the strictest sense there does not appear to be a functional correlate of the right stellate cardiac nerve to the atrioventricular junction. Such a nerve would produce a highly localized effect on atrioventricular conduction with little effect on heart rate or contractility. However, the nerves which elicit large dromotropic responses also innervate substantial areas of the atrial and ventricular musculature. These nerves are the ventrolateral cardiac nerve and the thoracic vagus on the left side and the right recurrent, craniovagal and caudovagal cardiac nerves and the thoracic vagus on the right side.

Although the ventrolateral cardiac nerve has been shown to elicit marked inotropic changes over much of the myocardium in addition to its effects on atrioventricular conduction, it does not seem to have a chronotropic effect at the sinoatrial node. Therefore, in a very loose sense, this nerve may be considered a positive dromotropic nerve, even though its distribution is not as limited as that of the right stellate cardiac nerve.

Since the nerves from the right side innervate the sinus node as well as the atrioventricular junction they provide a 'balanced' neural input to the pacemaker and conductile tissues. This balance may play an important role in matching atrial and ventricular rates known to occur under normal conditions. As stated by Hoffman and Cranefield (11) "the duration of atrioventricular delay is adjusted to changes in heart rate by activity of the vagus and sympathetics". This adjustment is necessary since an increase in heart rate per se slows conduction velocity through the atrioventricular junction (1,21) and thus may limit the ability of the ventricle to keep pace with an increased atrial rate.

Stimulation of the ventrolateral cardiac nerve provides a situation in which there is an 'imbalanced' neural input to the heart. Overactivity of the ventrolateral cardiac nerve could produce marked changes in atrioventricular automaticity and conduction while sinoatrial nodal changes would be minimal. A marked imbalance would result. The effects of such a situation were studied by Hageman et al. (9) and Randall et al. (30) utilizing a canine model in which the sinoatrial node and atrial tissues were totally denervated while the A-V junction and left ventricular myocardium retained their innervation via the ventrolateral cardiac nerve. The dogs were subjected to severe exercise in order to determine the effects of elevated sympathetic activity on the A-V conduction system. Reproducible tachydysrhythmias were elicited in all 6 animals studied. In addition abnormal rhythms consisting of shifting cardiac pacemakers and supraventricular junctional and ventricular tachycardias with frequent premature systoles were observed. Thus, autonomic imbalance is capable of producing cardiac arrhythmia.

To date other models of 'imbalance' have not been developed or studied. However this study would suggest that removal of the ventrolateral cardiac nerve input (decreasing sympathetic input or allowing unopposed parasympathetic input) to the atrioventricular junction may result in mismatching of atrial and ventricular rate. Removal of the parasympathetic activity to the atrioventricular junction would result in an imbalanced state with low parasympathetic, high sympathetic activity to the atrioventricular junction.

It is possible that such mismatching of atrial and ventricular rates do occur under normal or pathological conditions but the

differences are too subtle to be measured without highly sensitive techniques.

## SUMMARY AND CONCLUSIONS

In summary, the dromotropic effects of the individual cardiac nerves at the atrioventricular junction were studied. From the results collected, the individual cardiac nerves were divided into groups based upon the magnitude or the autonomic composition of the responses elicited.

Dividing them by their autonomic composition produces three categories; sympathetic, parasympathetic and mixed input to the atrioventricular junction. The sympathetic nerves were the left and right ansae subclavia, the ventrolateral cardiac nerve, the right stellate cardiac nerve and the innominate cardiac nerve. The parasympathetic nerves were the right and left thoracic vagi and the mixed nerves were the ventromedial cardiac nerve, the craniovagal and caudovagal cardiac nerves and the right recurrent cardiac nerve.

Dividing the individual cardiac nerves by the magnitude of the response they elicited produces two categories; major and minor effects on atrioventricular conduction. The cardiac nerves eliciting a major response were the left and right ansae subclavia, the ventrolateral cardiac nerve, the right recurrent cardiac nerve, the craniovagal cardiac nerve, the caudovagal cardiac nerve and the left and right thoracic vagi. Theoretically, the nerves of the right side, because of their innervation of both the sinoatrial node and the atrioventricular node, should produce a balanced heart rate-atrioventricular conduction response when stimulated. This would aid in matching atrial and ventricular rates. On the other hand, stimulation of the ventrolateral cardiac nerve has been shown to produce

arrhythmia. Although primarily due to increased automaticity at the atrioventricular junction, the production of these arrhythmias indicate the possibility of imbalanced autonomic activity in arrhythmogenesis. Because the ventrolateral cardiac nerve has little chronotropic effect at the sinoatrial node it may be considered a positive dromotropic nerve. However, its possible role in heart rate-atrioventricular conduction mismatching has not yet been delineated.

Only three cardiac nerves fit into the category of producing little or no effect on atrioventricular conduction. These are the innominate cardiac nerve, the ventromedial cardiac nerve, and the right stellate cardiac nerve. Because of its limited distribution and marked heart rate effects the right stellate cardiac nerve can be considered a positive chronotropic nerve. Its possible role in heart rate-atrioventricular conduction mismatching has not been delineated either.

All of the changes in conduction time elicited during cardiac nerve stimulation were seen during the A-H interval. Thus, this study supports the data suggesting that the autonomic nervous system has little dromotropic effect on the His-Purkinje conduction system (H-V interval).

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