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The Effects of Left Stellate Ganglion and Ventrolateral Cardiac Nerve Activity on Canine AV Nodal Electrophysiologic Properties

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THE EFFECTS OF LEFT STELLATE GANGLION AND VENTROLATERAL CARDIAC NERVE ACTIVITY ON CANINE AV NODAL ELECTROPHYSIOLOGIC PROPERTIES

by

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VITA

The author, David Leon Fishman, is the son of Jerry and Fanchon Fishman. He was born November 10, 1944, in Chicago, Illinois.

He received his elementary education in the public schools of Chicago, Illinois, and secondary education at Lane Technical High School, also in Chicago, Illinois, where he graduated in 1962.

In September 1962 he entered Loyola University and received a Bachelor of Science degree in June 1966 with a major in biology. David married Madelyn Levy in July, 1966. They have two children, Jennifer Mia and Zachary Michael. He then attended the University of Illinois College of Medicine, and in 1970 graduated with a degree of Doctor of Medicine. He was elected a member of Alpha Omega Alpha in 1970. In June 1970 he began an internship in Internal Medicine at the University of Illinois Affiliated Hospitals which was completed in June 1971.

From July 1971 to July 1973 he was a Captain in the Medical Corps of the United States Army. In July 1973 he returned to the University of Illinois Affiliated Hospitals

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His publications include the following:

1. Fishman, D.L.: On the usefulness of the Armed Forces physical examination. Current Medical Dialog 39: 613, 1972.

2. Fishman, D., Moran, J., Randall, W. and Gunnar, R.: Effect of left sympathetics on AV nodal conduction properties. Clin. Res. 25:221A, 1977.

3. Randall, W.C., Thomas, J.X., Euler, D.E. and Fishman, D.L.: Differential denervation of the SA and AV junctional regions in the chronic canine model. The Physiol. 20:77, 1977.

4. Fishman, D.L., Moran, J.F., Randall, W. and Gunnar, R.: Sympathetic modulation of canine AV nodal conduction properties. Circulation 56(Supp III) 81, 1977.

5. Moran, J.F., Fishman, D.L., Scanlon, P.J., Johnson, S.A., Tobin, J.R. and Gunnar, R.M.: EKG of the Month, Co-Editor, Illinois Medical Journal, September 1977 to present.

6. Pifarre, R., Montoya, A., Bakhos, M., Fishman, D., Scanlon, P. and Gunnar, R.: Poppet embolization from Braunwald-Cutter aortic valve. J. AM. Med. Assoc. 238: 2057, 1977.

7. Nemickas, R., Fishman, D., Killip, T., Dalton, W., Brynjolfsson, G., Robinson, J. and Gunnar, R.: Massive myocardial necrosis in a young woman. Am. Heart J. (In press).

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INTRODUCTION

Hoffman and Cranefield defined the general characteristics and function of the AV node and its relationship to the autonomic nervous system in 1960.

"The functional peculiarities of the atrioventricular node are numerous and diverse, and their consequences are often thought of more or less teleologically. Transmission of excitation from atrium to ventricle is delayed during passage through this structure, and the duration of this delay is adjusted to changes in heart rate by activity of the vagus and sympathetics. Atrial impulses are transmitted through the node only up to a certain frequency; above this limiting value increasing degrees of block and complete failure of transmission develop. The spread of excitation through the node results in simultaneous excitation of the fibers of the His bundle and thus permits almost synchronous activation of the mass of ventricular muscle. In the absence of a more rapid pacemaker the atrioventricular node may take over the function of impulse initation."[1]

The origin and course of the autonomic nerves distributed to the heart in the dog has been well described. In the modern era it was Nonidez[2] who delineated the general plan of the sympathetic and parasympathetic nerves to the heart; however it was Mizeres[3,4] who completely illustrated the anatomy of the intrathoracic cardiac nerves in the dog and unified the previously used nomenclature. Mizeres described the stellate ganglia, the ansa subclavia, the caudal cervical ganglion and the ventrolateral (cervical) cardiac nerve among others. His description and nomenclature are now in standard usage.

Mizeres also attempted to delineate the course and function of various cardiac nerves, specifically the acceler-

ator fibers. Although he did not state that he compared the left stellate ganglion to any of its subdivisions, he concluded "... The majority of sympathetic fibers carried by these nerves, specifically the ventrolateral cardiac nerve, are augmentor fibers which act to increase the force of the heart." Although vague, this represents the first comparisons of the left stellate ganglion to the ventrolateral cardiac nerve.

Geiss, et al.,[5] in 1973 described the major autonomic pathways to the AV node in the canine heart. Geiss, et al., concluded that their structure-function experiments demonstrated the AV nodal region is innervated by sympathetics from the right side by nerves that course along the great vessels and at the junction of the inferior vena cava with the left atrium and that the left sided sympathetic nerves reach the nodal region along similar pathways as well as the ventrolateral cardiac nerve. These earlier publications demonstrate the relationship of atrioventricular function and the intrathoracic sympathetic nervous system anatomy. Details of this relationship will be described in the literature review.

Left Stellate Ganglion

In 1964, Wallace and Sarnoff[6] and Sarnoff, et al.,[7] studied the effects of cardiac sympathetics on conduction in the heart. They were concerned with the possibility that sympathetic stimulation increased ventricular myocardial synchronicity and altered intra-atrial and atrioventricular conduction. They hoped to determine that sympathetic stimulation not only produced a stronger contraction of each cardiac muscle fiber from any given fiber length, but also produced a more synchronous ventricular contration of these augmented myocardial fibers.

Sarnoff, et al.,[7] and Wallace and Sarnoff[6] studied adult mongrel dogs under pentobarbital anesthesia. In addition to bilateral vagotomy, each animal had the left stellate ganglion isolated. Stellate stimulation parameters sited were 8 volts at 10 Hz. The duration of the stimulation was not specified. The dogs were also paced with an atrial catheter at a rate of 196 beats/minute. The experimental protocol measured atrial activity from the low right atrium, the His electrogram, ventricular electrograms, and the surface electrocardiograms, as well as measurement of ventricular pressure and aortic pressure.

In the portion of the study which measured atrioventricular conduction, the control AH interval had a mean value of 62.4 msec and the AH interval following stellate ganglion stimulation was 31.3 msec, representing a decrease of 48.8%.

They concluded that this finding demonstrated enhanced conduction through the AV node and was consistent with their observation that left stellate ganglion stimulation shortened the PR interval on the surface electrocardiogram, as well as the interval between the mechanical events of atrial and ventricular systole. In other words, left stellate stimulation reduced AV nodal delay. In other portions of the conducted experiments Wallace and Sarnoff noted a consistent decrease in total ventricular activation time. They accounted for such changes on the basis of more rapid transmission through the ventricular muscle. In contrast they noted that conduction through the Purkinje system appeared to be unaltered by sympathetic stimulation. They suggested therefore, that changes in synchronicity of contraction occur as a result of sympathetic stimulation, but not as a consequence of altered electrical activation within the specialized conduction tissue, but rather as a result of more rapid transmission through ventricular muscle.

The conclusions of Wallace and Sarnoff were consistent with those of Carlen and Katz[8]. In 1939 Carlen and Katz compared the ventricular response rate during control and stellate stimulation in animals who underwent artificially induced atrial fibrillation. The control rates for ventricular response were approximately 230 beats/minute and the result of stellate stimulation yielded heart rates of

approximately 310 beats/minute. Carlen and Katz concluded that sympathetic stimulation enhanced AV conductivity. They did not site the parameters for their stellate stimulation, nor did they measure any intracardiac electrical impulse or conduction activity.

Three articles appeared in the French literature, Arnould, et al.,[9] and Duchene-Marullaz, et al.,[10,11] in the middle 1960's comparing the effect of left and right stellate ganglia stimulation on increasing the maximal paced rate obtainable, compared to the resting state. The dogs were maintained on volatile anesthesia and a respirator. In the series of experiments conducted, involving stimulation of the left stellate ganglion the authors noted a maximum conducted heart rate in the unstimulated animal of approximately 260 beats/minute. Stimulation of the left stellate ganglion increased the maximal conducted heart rate to 360 beats/minute. These authors did not verify their surface recording with intracardiac recordings to determine whether or not intermittent AV block was present.

In 1969, Levy and Zieske[12] conducted experiments on mongrel dogs under chloralose anesthesia. They attempted to quantitate the interactions of autonomic control on cardiac pacemaker activity and atrioventricular conduction. The protocol used involved stimulation of the right stellate ganglion and the left vagosympathetic trunk. A major objective of their experiments was to compare the effect of sym-

pathetic and parasympathetic interaction on pacemaker activity and atrioventricular conduction; however in establishing parameters for the interaction the authors performed isolated stellate stimulation and observed that stimulation of the sympathetics decreased the PR interval on the surface electrocardiogram.

In 1971, Irisawa, et al.,[13] studied atrioventricular conduction in mongrel dogs under pentobarbital anesthesia. These workers stimulated the left stellate ganglion with 7 volts at 7 to 10 Hz, (the duration was not specified) and measured an electrogram obtained from isolated atrial and ventricular electrodes during left stellate stimulation. They noted approximately a 19% reduction in the interval between atrial and ventricular electrograms during sympathetic stimulation. The results of their study cannot be directly compared to those of Wallace and Sarnoff because the hearts were not paced at a constant rate and their percentage reduction was compared to atrioventricular conduction, rather than AV nodal conduction, however, they did confirm that left stellate stimulation decreases AV nodal conduction time.

Priola[14] in 1971, during a study of the effects of beta receptor stimulation and blockade noted that stellate ganglion stimulation reduced the AH interval by 26% from a control of approximately 53 msec to 39 msec. The dogs in this series of experiments were anesthetized with sodium pen-

tobarbital, and the electrodes used for obtaining electrograms were placed during total cardiopulmonary bypass. The stimulation frequencies were 10 Hz at 5 msec duration.

Spear and Moore[15] (1973) studied the effect of stellate and vagal nerve stimulation on pacemaker activity and conduction within the atrioventricular conduction system of the dog. These investigators stimulated the right stellate ganglion, and concluded that stellate stimulation enhanced AV nodal conduction. They did not stimulate any of the left sided sympathetics, nor compare responses during excitation of subdivisions of the stellate ganglia.

Goldberg and Randall[16] studied left stellate stimulation in mongrel dogs anesthetized with alpha chloralose. The study was designed to determine the effect of stellate stimulation on internodal and AV nodal pathways. Prior to the measurements the dogs had been on cardiopulmonary bypass for the purpose of placing the electrodes. The left stellate ganglion was stimulated at 10 Hz, 10 msec, and 5 to 7 volts. The dogs were studied while paced at a rate of 300 beats/minute and also whil unpaced. The authors noted a reduction of 27 and 35% in the AH interval in these respective groups. They did not study the effects of subdivisions of the left sided sympathetic nervous system.

Ventrolateral Cardiac Nerve

In 1973, Armour, et al.,[17] and Hageman, et al.,[18] studied the cardiac arrhythmias induced by stimulation of

local cardiac nerves. Included in their study was the effect of stimulation of the ventrolateral cardiac nerve. In addition to multiple arrhythmias and alterations in contractile force, these workers noted that excitation of the ventrolateral cardiac nerve reduced the AH interval of the intracardiac electrogram. These authors also noted shortening of the HV interval on the above electrogram and noted that the effect was present even when the dogs were decentralized via isolation of the stellate ganglia and cervical vagotomy.

Electrophysiology

In 1968, Scherlag, et al.,[19] recorded the electrical activity from the His bundle of the intact dog, using a multipolar catheter containing three bipolar recording/stimulating bands to record the activity from the His bundle. One year earlier Scherlag, et al.,[20] had used fine wire electrodes inserted into the region of the AV node to record this phenomenon; however, this procedure required thoracotomy. The technique described in 1968 required placement of the previously mentioned catheter across the tricuspid valve. Shortly thereafter His bundle recordings were obtained in man by Scherlag, et al.[21]

In 1972 Scherlag, et al.,[22] demonstrated that the AH interval represented an accurate measurement of electrical transmission and conduction through the AV node, since the A

wave of the His bundle electrogram represented local atrial activity in the vicinity of the AV node. This direct measurement eliminated intraatrial conduction between SA node and the low right atrium. In addition, the AH interval allowed a comparison of AV nodal conduction time during both sinus rhythm and during atrial pacing because the low atrial deflection used in measurement was not altered by the pacing site. This was in contrast to those techniques which measured the PH interval (beginning of the P wave on the surface electrogram to the H spike on the intracardiac electrogram), which could not be accurately compared, because the pacer impulse was not applied to the site of spontaneous impulse formation (i.e., the sinus node).

In 1971 Scherlag, et al.,[23] demonstrated that His bundle records could be obtained from a catheter introduced through the peripheral arteries and directed into the aortic root, with the tip lodged in the noncoronary cusp of the aortic valve and in close apposition to the His bundle. Electrograms obtained in this method compared favorably with those of the venous method with the catheter lying across the tricuspid valve. This approach was found to be more useful to the authors, because of the rapidity in obtaining consistently high fidelity records and well as in long term stability of the catheter in this position.

Narula[24] listed the technique for validation of His

bundle recordings. He stated the most important corroboration that the electrophysiologic activity monitored is originating from the His bundle was by simultaneously recording more than one peripheral EKG lead during pacing from the His bundle recording site with maintenance of a narrow QRS complex. This indicated that a bundle branch or ventricular musculature was not being stimulated, (i.e., stimulation of a bundle branch or ventricular musculature would produce a wide QRS complex).

In 1975 Reddy et al.,[25] demonstrated that the intracardiac electrogram intervals (AH and HV) were reproducible at 30 and 60 minute intervals, with no statistically significant changes from control, and in AV conduction time in patients who were either normal volunteers or undergoing His bundle studies for clinical conditions.

In 1975 Wu, et al.,[26] summarized and defined the refractory periods of the atrioventricular conduction tissue.

"...refractory periods of different conduction tissues at several levels can be determined by the atrial extra stimulus technique and with His bundle recording. With this technique, an atrial extra stimulus (S_2) is applied at decreasing coupling intervals after a series of atrial driven beats. The stimulus artifact (if the atria are driven with atrial pacing), atrial electrogram, His bundle electrogram and ventricular electrogram of driven beats are labeled S_1, A_1, H_1 and V_1. The respective responses to the extra stimulus are labeled A_2, H_2, and V_2. S_2 is brought closer to the last driven beat until S_2 fails to propagate to the atrium.

Refractoriness of a tissue can be expressed with two measurements ... the functional refractory period of a tissue is the shortest obtainable interval between two impulses, the basic and the premature, traversing that tissue and is mea-

sured at a point distal to the tissue. The effective refractory period of a tissue is the longest interval between two impulses, the basic and the premature, where the premature, impulse fails to traverse the tissue and is measured proximal to the tissue. These relationships can be examined by plotting a curve relating the output and input intervals. For example, in the AV node if H_1-H_2 are the His bundle responses (output) and A_1-A_2 are the atrial coupling intervals (input), AV nodal functional refractory period is the shortest obtainable H_1-H_2, and AV nodal effective refractory period is the longest A_1-A_2 where A_2 is not followed by an H_2 (Figure 1)."

Wu, et al.,[26] went on to demonstrate that the refractory period of the atrial-ventricular conduction system is frequency dependent. However, this had been previously demonstrated by Mendez, et al.,[27] who demonstrated that the functional refractory periods of the AV node, atrium, and ventricle shortened as the cycle length decreased. The changes induced by shorter cycle lengths in the refractory periods were most striking in the His-Purkinje system and least apparent in the AV node, but they were in fact present in the latter.

FIGURE 1

AV Node Refractory Periods

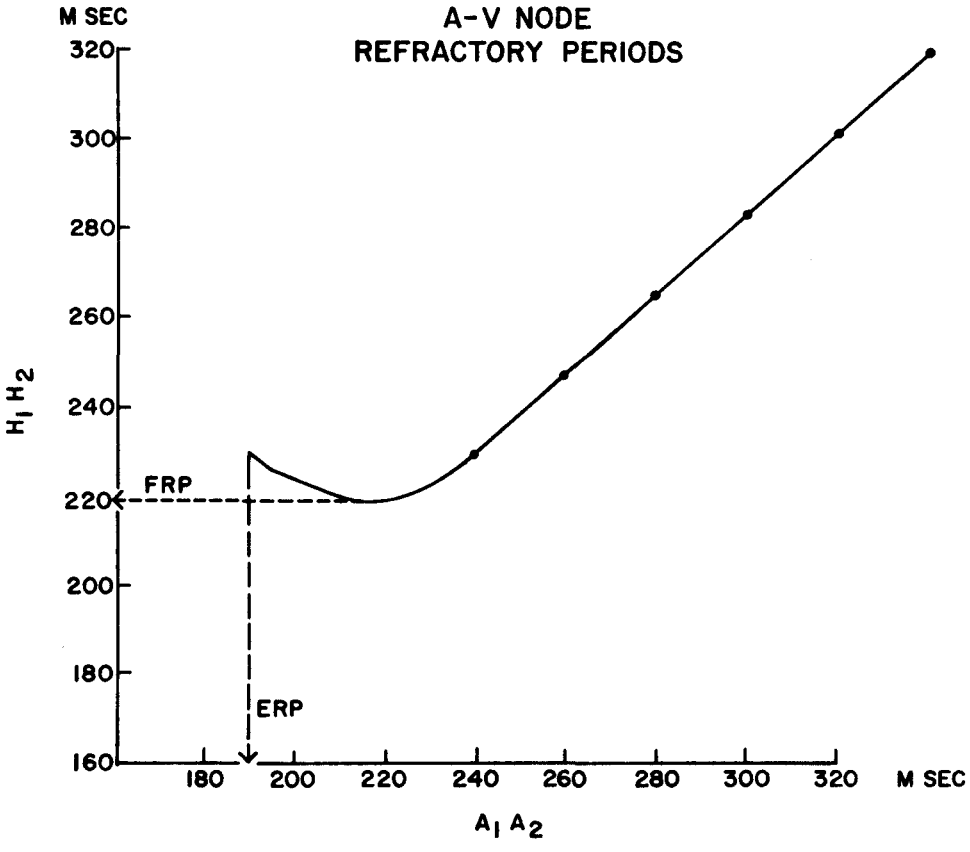

FIGURE 1

Diagramatic representation of A_1-A_2, H_1-H_2 curve showing functional refractory period, (FRP) and effective refractory period (ERP) of the AV node. H_1-H_2 on the ordinate is plotted as a function of A_1-A_2 on the abscissa. The units on the ordinate and abscissa are msec (Adapted from Wu, et al.[26]).

Anesthetic Agents

Alpha chloralose was selected as the anesthetic agent because previous workers have noted that alpha chloralose slightly increases the excitability of the sympathetic nervous system[28]. Whereas other agents, most notably pentobarbital, have a direct myocardial depressant effect and these agents also depress automaticity and conductivity[29,30].

Statement of Purpose

The purpose of the experiments conducted was to determine the effect of left stellate ganglion and ventrolateral cardiac nerve stimulations on AV nodal conduction. The measurements chosen to determine the effect of stimulation were the maximum conducted heart rate while pacing, and the changes in functional refractory period and effective refractory period of the AV node during control and stimulation.

In addition, the effect of the ventrolateral cardiac nerve was determined by measuring the maximum conducted heart rate before and after transection. The protocol in the following section also allows for evaluation of the effect of left stellate ganglion and ventrolateral cardiac nerve stimulation at graded pacing intervals during stimulation and also following transection of the ventrolateral cardiac nerve.

EXPERIMENTAL DESIGN

Preparation

Twenty-eight adult mongrel dogs, weighing between 15 and 25 kg were studied in two different protocols. The dogs were sedated with 1.0 mg of phencyclidine hydrochloride and anesthetized with alpha chloralose 80 mg/kg. A tracheostomy was performed or the dogs were intubated with an endotracheal tube and supported on a Bird #7 positive pressure respirator at 40% O_2 mixture. Bilateral thoracotomy was performed and the left stellate ganglion and the ventrolateral cardiac nerve were isolated and prepared for stimulation. The vago-sympathetic trunks as well as the white rami remained intact.

A small pericardiotomy was performed and plunge electrodes were placed in the high right atrium and in the left ventricle to obtain electrograms from these locations. The pericardiotomy was then sutured. His bundle electrograms were obtained with a bipolar electrode catheter in the non-coronary cusp of the aortic valve, placed through the right common carotid artery. Pacing from the site of recording and observing a narrow QRS complex and a stable HV interval with pacing and extra stimulus technique confirmed the identity of the His electrogram. Electrograms were recorded on a multichanneled oscilloscope recorder (Electronics for Medicine) at a paper

speed of 200 mm/sec. Pacing stimuli were rectangular waves, 3 msecs in duration, 2 to 3 times threshold intensity and originated from an electronic stimulator (Grass Model SD 9 or S 88). Nerve stimulation was accomplished at 10 volts, 10 msec, 10 Hz for 10 seconds with an electronic stimulator (Grass Model 55). Stimulation of the left stellate ganglion was applied directly to the main body of the left stellate ganglion, and stimulation of the ventrolateral cardiac nerve was applied 1 cm distal to the caudal cervical ganglion (Figure 2). All equipment was properly grounded and isolated. All dogs had normal AH and HV intervals [6,7,5,16] and blood pressure before the actual electrophysiologic protocol was begun.

Electrophysiologic Protocol

Group IA

The right atrium of each of 20 animals was paced at increasing rates, from 150/minute (cycle length 400 msec), until the occurrence of second degree AV block (Type I, Wenckebach). Rates were successively increased at 15 stimuli per minute increments. This phase served as a control for Group IA animals. The control was repeated in 15 stimuli per minute decrements and 10 minutes after all nerve stimulations. The hearts were then again paced in ascending fashion during ventrolateral cardiac nerve stimulation and during left stellate ganglion stimulation.

FIGURE 2

Left Sided Intrathoracic Autonomic Nerves

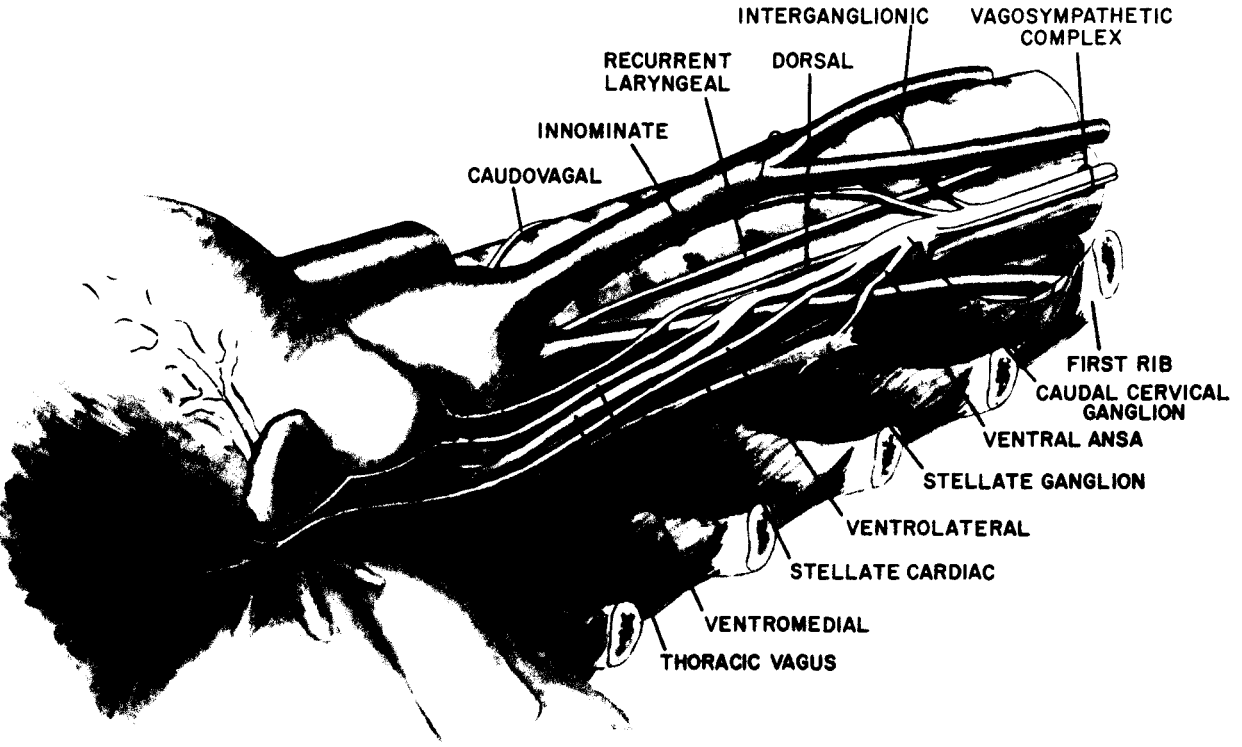

FIGURE 2 [31]

Left sided canine cardiac nerves shows how the ventrolateral cardiac nerve arises from the inferior lateral aspect of the caudal cervical ganglion.

Group IB

Each of 11 animals, some of which were included in group IA followed the protocol in IA, however, additional data were then obtained. The ventrolateral cardiac nerve was transected and control and left stellate ganglion stimulations were repeated.

Group II

This group of 9 animals was prepared in the same fashion as Group I. Then the right atrium was paced at a constant rate of 165 beats/minute from the high right atrial electrode (cycle length 364 msec). This rate was selected to maintain capture during subsequent ventrolateral cardiac nerve and left stellate ganglion stimulation. Increasingly premature atrial beats were then programmed until the absolute refractory period of the atrial tissue was reached. The premature beat was always preceeded by at least 10 beats of the basic driving rate. This process was then repeated during left stellate stimulation and during ventrolateral cardiac nerve stimulation. These data were then plotted on a curve similar to that of Wu, et al.,[26] and the effective and functional refractory periods were determined.

Statistical Analysis

The p values for all comparisons were determined by two-tailed t test, paired data difference method; except those comparisons of effective and functional refractory period

which were determined by two-tailed signed rank test of Wilcoxon[32].

RESULTS

Control

As described above, a control was obtained during ascending and descending pacing sequences, and following sympathetic stimulation. The maximum paced rate that was conducted 1:1 during the control period had no statistically significant difference whether obtained ascending, descending or in the recovery period, 10 minutes following sympathetic stimulation. The mean cycle length for maximum paced rate for ascending control was 209 msec. The average obtained for descending was 208 msec, and the average obtained following sympathetic stimulation was 210.2 msec (p for all comparisons > 0.8).

The AH intervals at all paced rates during control, no matter in which fashion they were obtained, were not statistically different. The AH intervals at maximum conducted paced rate for all the controls were also similar to each other. They were respectively 120.7 msec for ascending, 119.7 msec for descending and 123.8 msec for those in the recovery period 10 minutes following sympathetic stimulation (p for all comparisons > 0.5). Because there were no statistically significant differences between any of the obtained controls, the mean control value was used as the "control" of each dog for all comparisons to sympathetic stimulation.

The control value for animals in Group II was not repeated following sympathetic stimulation.

Left Stellate Ganglion Stimulation

The maximum paced rate conducted 1:1 increased by an average of 39.9 beats during left stellate ganglion stimulation compared to control (group IA), control rate 274.6 beats/minute cycle length 218.5 ± 6.8 msec, left stellate ganglion stimulation rate 314.5 beats/minute, cycle length 190.8 ± 5.4 msec) ($p > 0.001$). The AH interval at all paced rates was significantly shorter during left stellate stimulation than during control ($p > 0.01$). Figures 3 and 4 graphically represent these comparisons.

Figure 5 demonstrates the typical result in a single experiment. In each panel the top wave forms represent surface leads of the electrocardiogram I, II, and III, the 4th line represents atrial activity. The fifth line is the electrical activity recorded from the His bundle electrode. S indicates the stimulus artifact in the right atrium; A is the atrial activity; H is the His bundle spike; and V is the ventricular activity. SS measures the time between stimulus artifacts; AA is time between atrial activations; AH the interval from atrial to His activations and HV the interval from His bundle electrical activity to ventricular activations. Figure 5 shows the control state in the upper panel, left stellate ganglion stimulation in the middle panel and ventro-

FIGURE 3

Heart Rate (Cycle Length); Control and Interventions

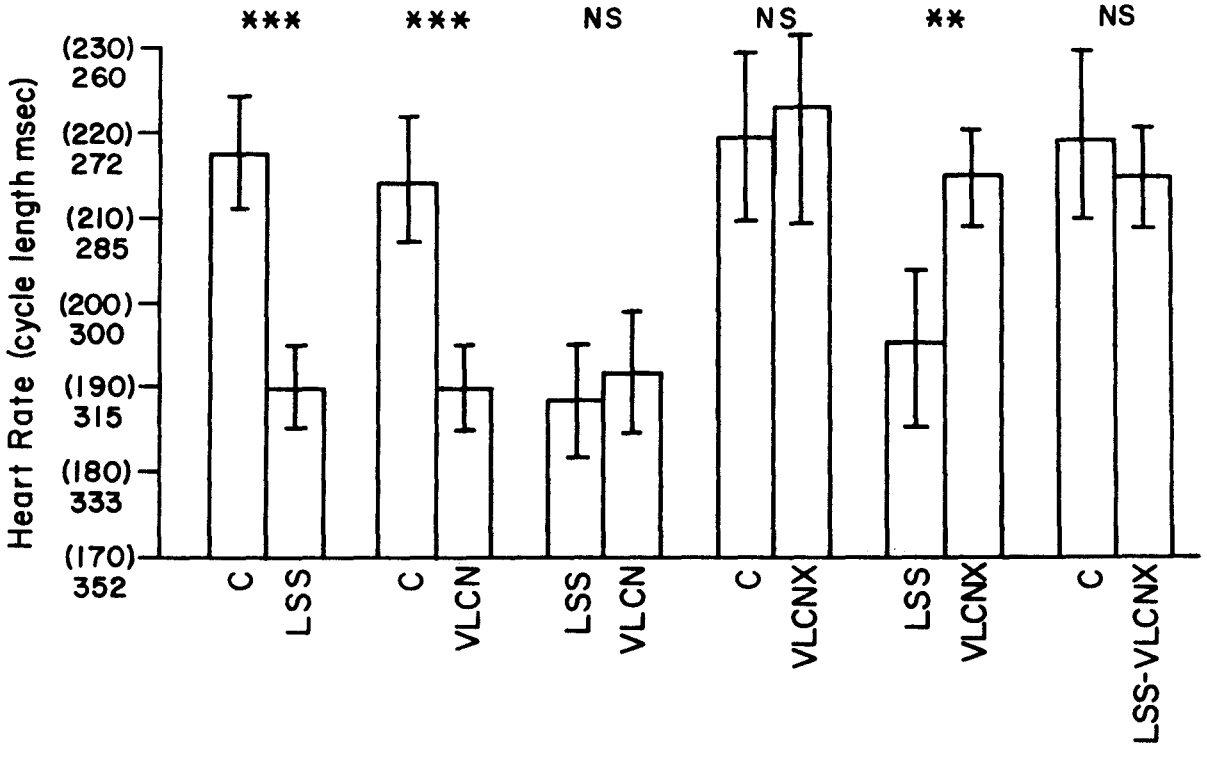

FIGURE 3

Comparison of maximum paced rate (cycle length in msec) of control and various interventions. C = control, LSS = left stellate ganglion stimulation, VLCN = ventrolateral cardiac nerve stimulation, VLCNX = left stellate stimulation after transection of the ventrolateral cardiac nerve, N = number of dogs (20 for control, 18 for VLCN, 11 for VLCNX and 8 for LSS-VLCNX.) Symbols: *** = $p < 0.001$, ** = $p < 0.01$ * = $p < 0.05$. NS = not sigificant.

FIGURE 4

AH Interval During Graded Pacing; Control, Left Stellate Ganglion and Ventrolateral Cardiac Nerve

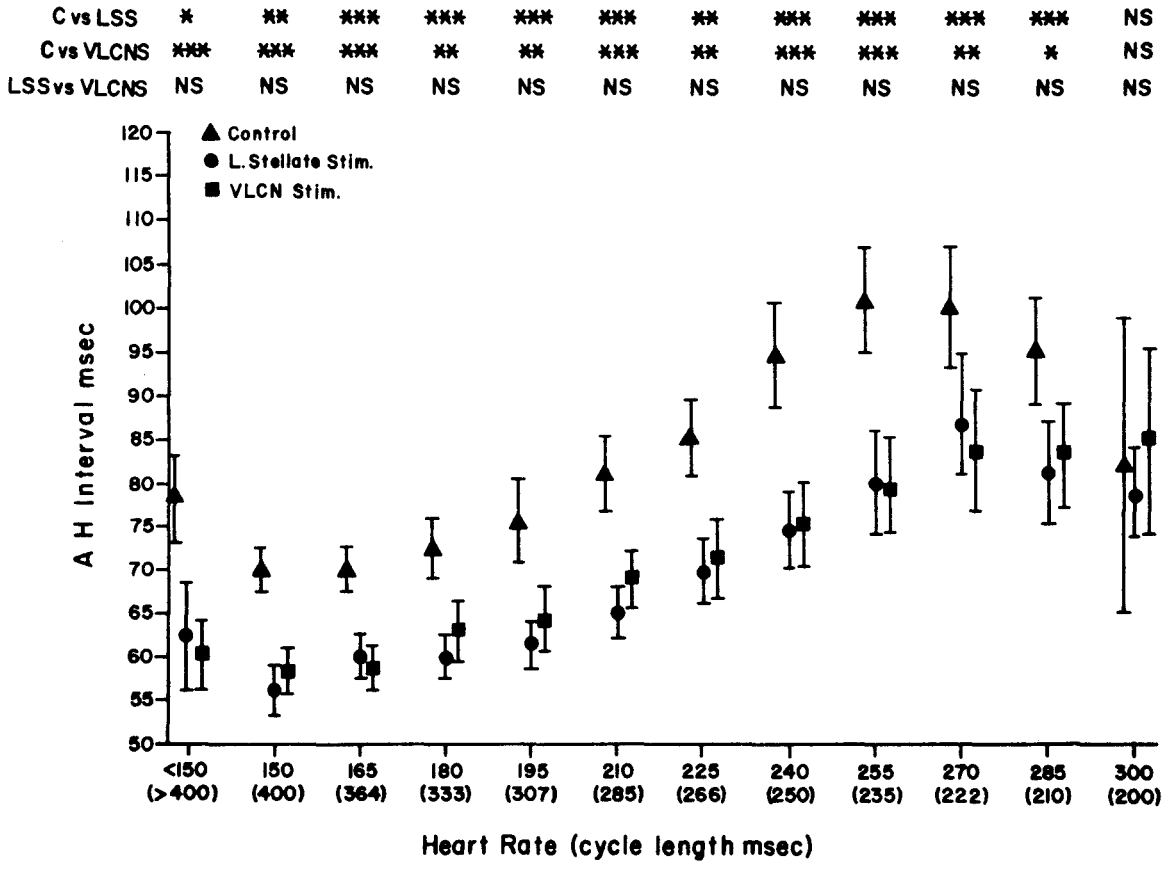

FIGURE 4

Comparison of AH interval at graded pacing rates (cycle length) for control, left stellate ganglion stimulation, and VLCN stimulation preparations. N - number of dogs compared for various cycle lengths as follows: > 400 msec N = 13, 364 msec N = 16, 333 msec N = 19, 307 msec N = 16, 285 msec N = 17, 266 msec N = 16, 250 msec N = 16, 235 msec N = 16, 222 msec N = 14, 210 msec N = 12, 200 msec N = 6. Symbols for statistical significance are the same as Figure 3.

FIGURE 5

Recording During Control; Left Stellate Ganglion Stimulation and Ventrolateral Cardiac Nerve Stimulation

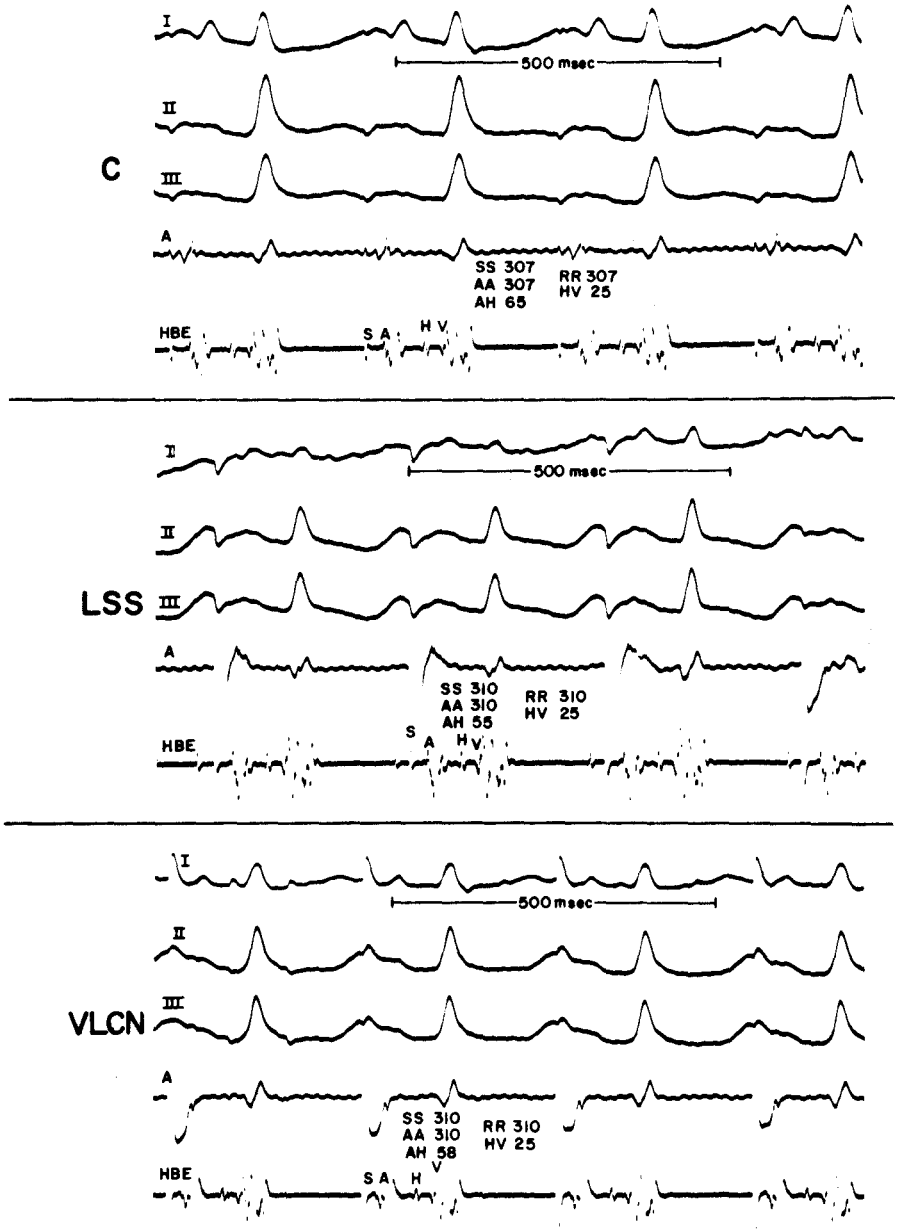

FIGURE 5

Upper panel shows surface leads I, II, and III, atrial electrogram and His bundle electrogram. S = stimulation artifact, A = atrial electrogram, H = His electrogram, V = ventricular activation, SS = interval between the stimulation artifacts, AH = time interval between atrial activation and HV = time from His bundle activation to ventricular activation. The control (C) panel on the top shows the normal electrograms. Left stellate stimulation (middle panel) demonstrates shortening of the AH interval from 65 msec to 55 msec with no change in the HV interval during the stimulation. Notice that SS interval is essentially unchanged. The lower panel shows the results of ventrolateral cardiac nerve (VLCN) stimulation at the same pacing interval, 310 msec. In this case the AH interval has shortened from a control of 65 to 58 msec. Notice once again that the HV interval is unchanged.

lateral cardiac nerve stimulation in the lower panel. In all three panels the SS interval is approximately the same as is the AA interval, however the AH interval is shortened considerably during left stellate ganglion stimulation and ventrolateral cardiac nerve stimulation and is without effect on the other measured intervals.

The AH interval at maximum conducted paced rate was similar for control and during left stellate ganglion stimulation (control 117.3 $\pm$ 5.3 msec; left stellate ganglion stimulation 113.2 $\pm$ 5.7 msec) ($p = 0.44$ as seen in Figure 6).

The effective refractory period and the functional refractory period (group II) of the AV node were reduced during left stellate stimulation by a mean difference of 12.5 msec and 23.6 msec respectively ($p > 0.01$ and > 0.01 respectively) (Figures 7 and 8 and Tables 1 and 2). Figure 9 is a representative graph of data obtained during a single experiment and demonstrates the effect of left stellate ganglion stimulation on the conduction of premature atrial beats introduced at progressively more premature intervals as described in the protocol.

Figure 10 demonstrates results of a premature atrial stimulus at a coupling interval of 240 msec following 10 beats at the basic driving rate (364 msec). The upper panel is the control tracing where the H_1, H_2 interval is 280

FIGURE 6

AH Intervals at Maximum Conducted Heart Rate; Control and Interventions

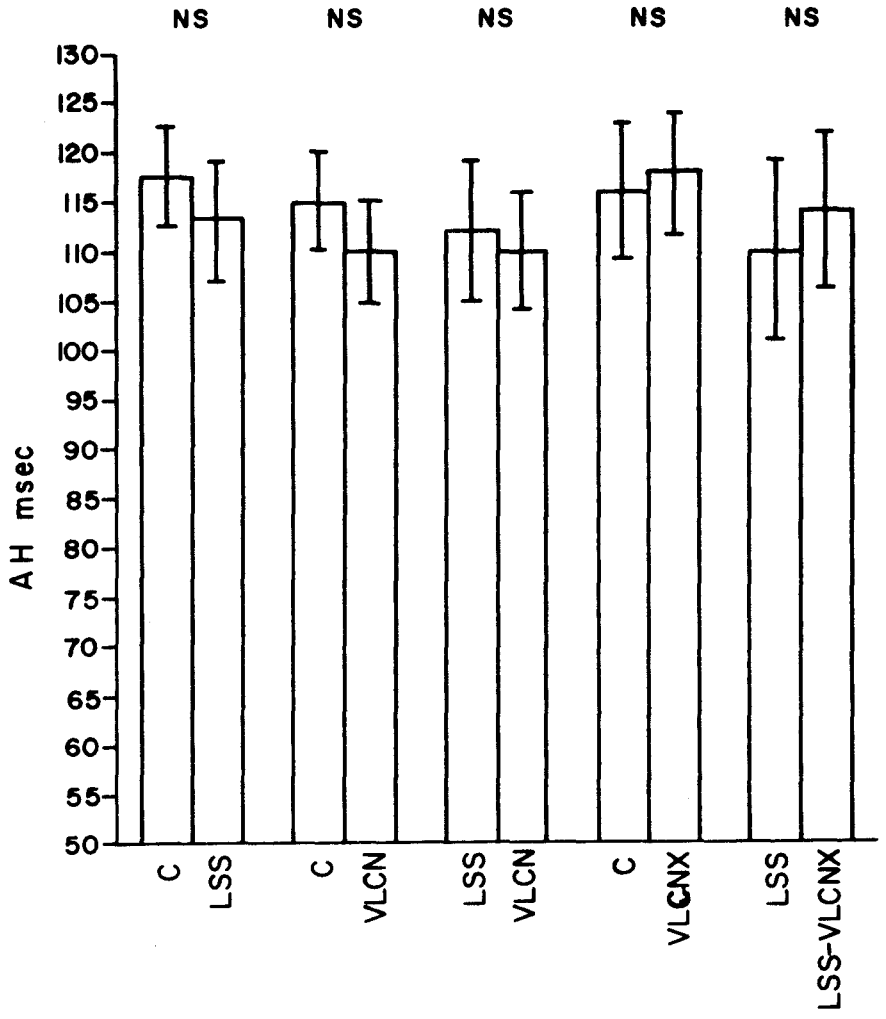

FIGURE 6

Comparison of the AH intervals; the units of measurement to the left are the AH interval in msec at the maximum conducted heart rate prior to second degree AV block. The N - number of dogs compared for the various groups: control 19, left stellate ganglion stimulation 19, ventrolateral cardiac nerve stimulation 18, ventrolateral cardiac nerve transection 11, left stellate stimulation with ventrolateral cardiac nerve transection 8. There is no statistical difference between the AH interval at maximum conducted heart rate whether during control, during intervention or after transection of the ventrolateral cardiac nerve.

FIGURE 7

Effective Refractory Period; Control, Left Stellate Ganglion Stimulation and Ventrolateral Cardiac Nerve Stimulation

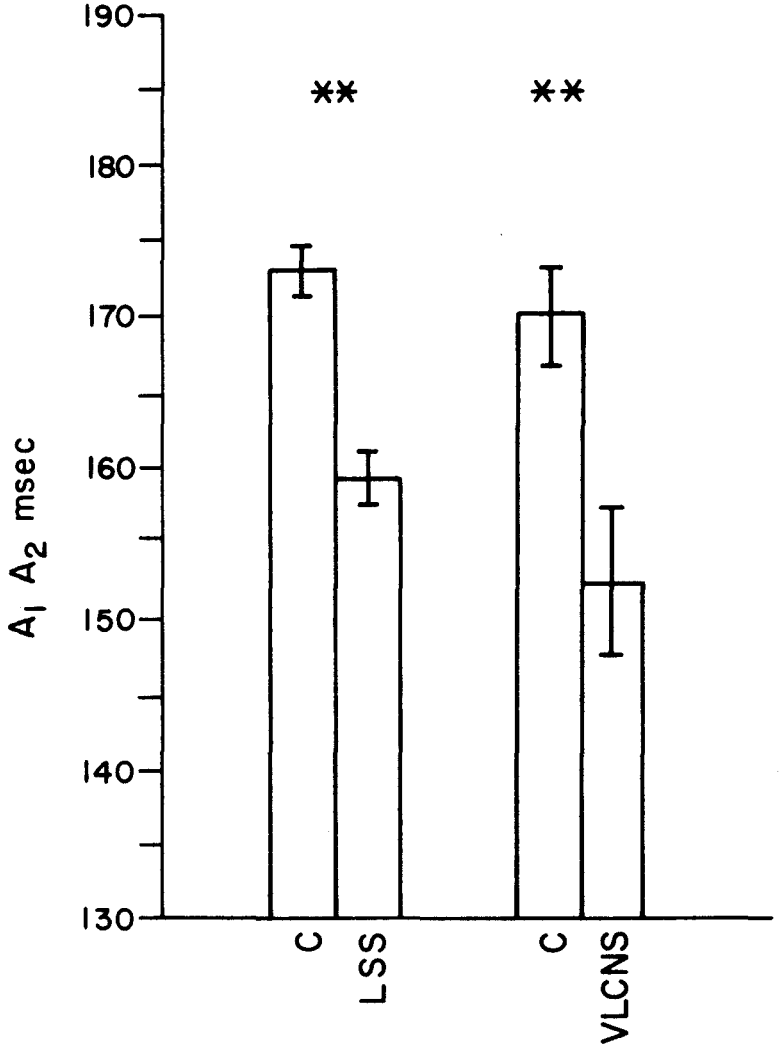

FIGURE 7

Graphic display of effective refractory period of AV node during control, left stellate stimulation and ventrolateral cardiac nerve stimulation. Symbols and abbreviation are the same as Figure 3. (Experimental data in Table 1)

TABLE 1

Effective Refractory Periods - A_1 A_2 msec

Experiment #	Control	LSS	VLCN
1	175	165	165
2	148	---	145
3	180	157	160
4	170	165	167
5	170	150	152
6	177	170	---
7	172	160	167
8	173	160	135
9	165	147	135
Mean ± SE	172.8 ± 1.5	159.3 ± 3.2	153.3 ± 4.5

p values

Control vs LSS < 0.01

Control vs VLCN < 0.01

LSS vs VLCN - NS

FIGURE 8

Functional Refractory Period: Control, Left Stellate Ganglion Stimulation and Ventrolateral Cardiac Nerve Stimulation

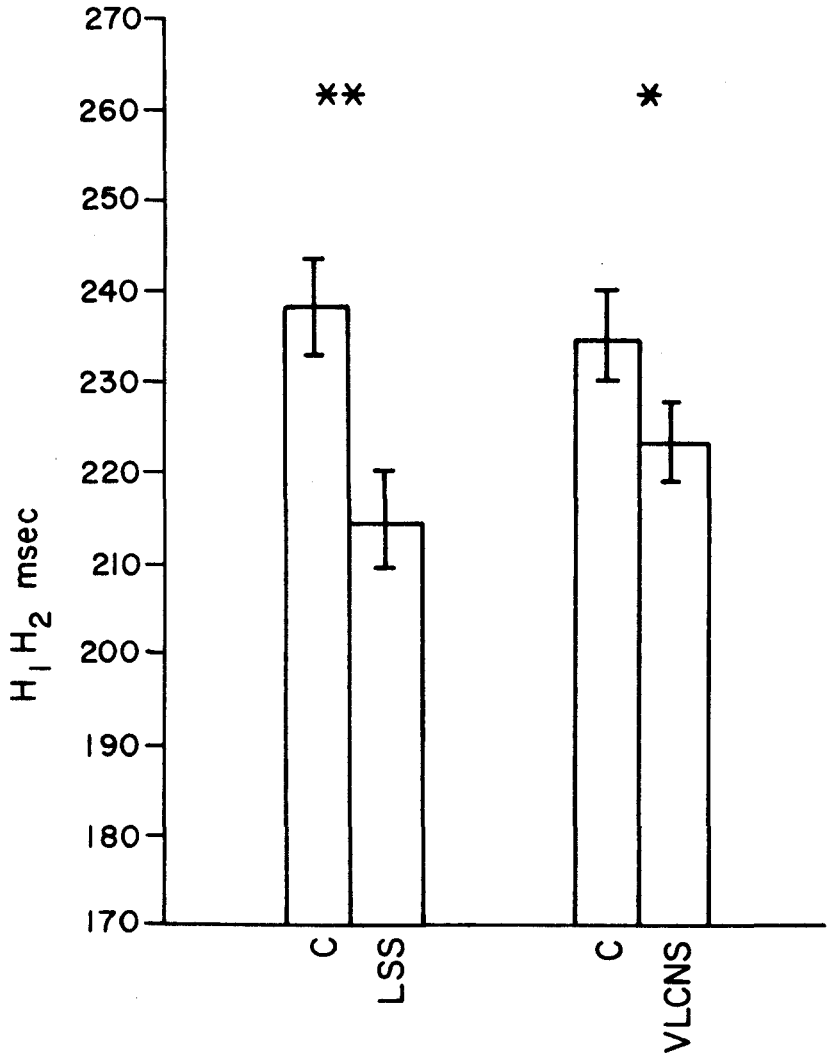

FIGURE 8

Graphic display of functional refractory period of AV node during control, left stellate and ventrolateral cardiac nerve stimulation. Symbols and abbreviations are the same as Figure 3. (Experimental data in Table 2)

TABLE 2

Functional Refractory Periods - H_1 H_2

Experiment #	Control	LSS	VLCN
1	242	240	220
2	220	---	200
3	225	220	225
4	218	207	220
5	217	220	225
6	257	175	252
7	240	225	230
8	265	215	215
9	242	210	230
Mean $\pm$ SE	238.3 $\pm$ 5.8	214.0 $\pm$ 6.2	224.1 $\pm$ 4.3

p values

Control vs LSS < 0.01

Control vs VLCN < 0.05

LSS vs VLCN - NS

FIGURE 9

Effective and Functional Refractory Periods, Experiment #7

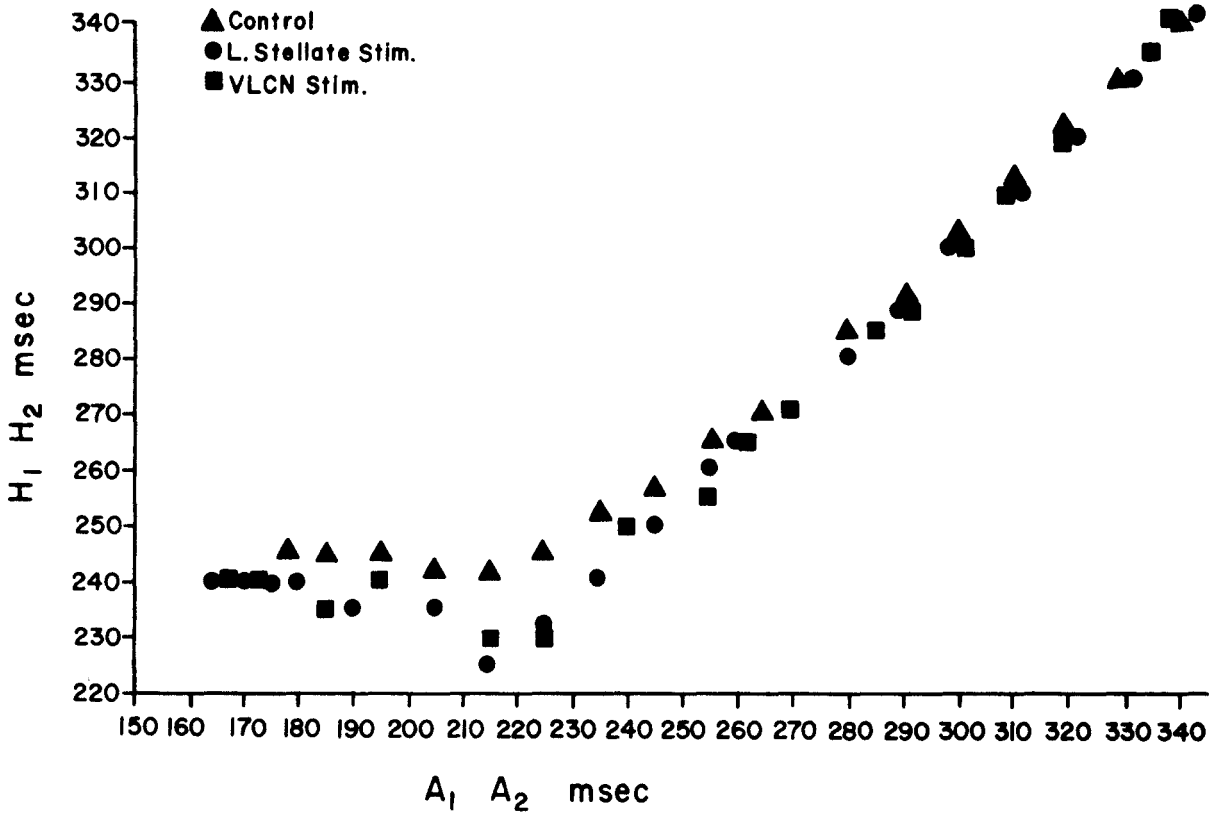

FIGURE 9

The results of control, left stellate ganglion stimulation, and ventrolateral cardiac nerve stimulation in a representative experiment (Experiment #7, group II). On the ordinate are the H_1, and H_2 interval in msec. On the abscissa are the A_1, and A_2 interval also in msec. Each symbol represents a premature atrial beat. Notice how left stellate ganglion stimulation and ventrolateral cardiac nerve stimulation shift the curve downward and to the left.

FIGURE 10

Recording of Atrial Extra Stimulus Technique; Control, Left Stellate Ganglion Stimulation and Ventrolateral Cardiac Nerve Stimulation

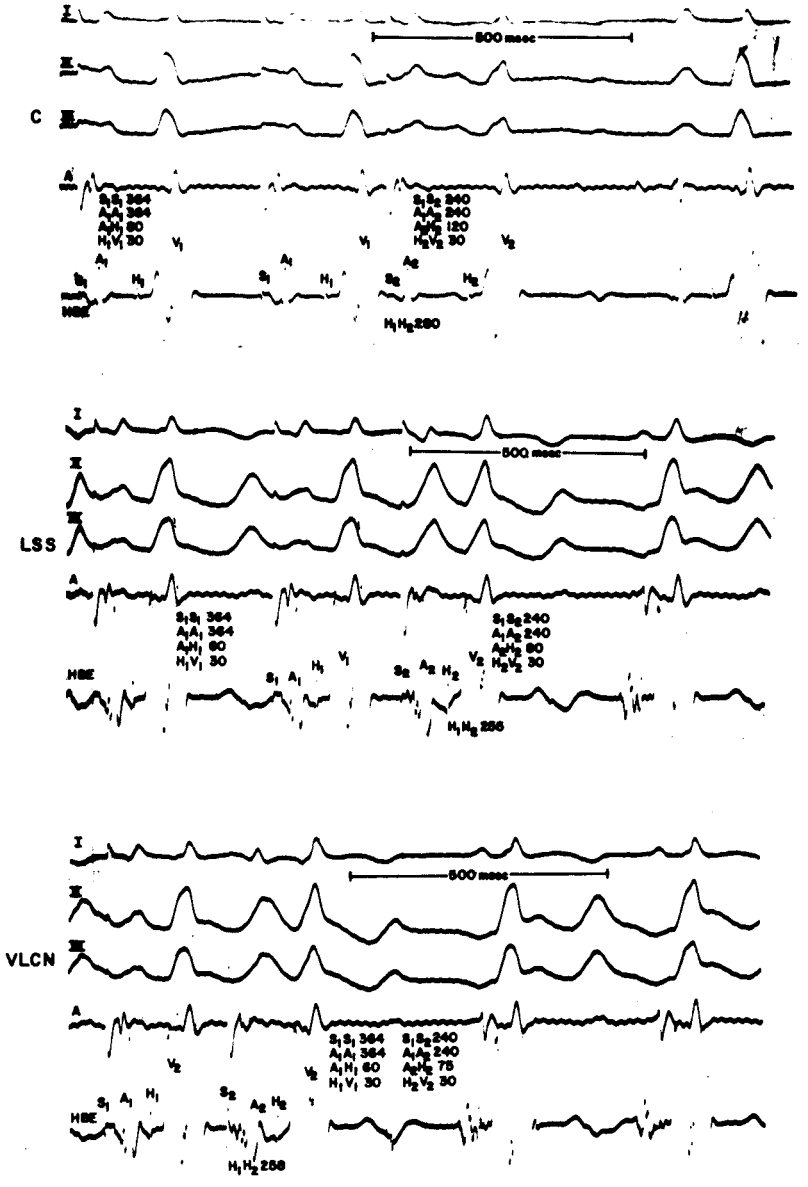

FIGURE 10

Abbreviations as per Figure 5. Upper panel (control) shows control H_1 H_2 of 280 msec with atrial extra stimulus at interval of 240 msec (A_1 A_2). Middle panel demonstrates decrease of H_1 H_2 interval to 255 msec at same coupling interval during left stellate stimulation, and lower panel shows decrease of H_1 H_2 interval to 258 msec at same coupling interval during VLCN stimulation.

msec. The middle panel is the same sequence during left stellate stimulation and the H_1, H_2 interval is reduced to 255 msec. The lower panel is the same sequence during ventrolateral cardiac nerve stimulation and the H_1, H_2 is reduced to 258 msec. S_1 = stimulus artifact from pacemaker, A_1 is the atrial electrogram in response to S_1, H_1 is the His electrogram in response to S_1, V_1 is the ventricular activation subsequent to S_1. S_2 is the stimulus artifact for the premature beat. A_2 is the atrial electrogram in response to S_2. H_2 is the His electrogram in response to S_2. V_2 is the ventricular activation subsequent to S_2. S_1-S_2 measures time (msec) between stimulus artifacts; A_1-A_2 time between atrial electrograms and H_1-H_2 time between His electrograms.

Ventrolateral Cardiac Nerve Stimulation

During ventrolateral cardiac nerve stimulation (group IA) the maximum paced rate that was conducted 1:1 was greater than control. The average increase was 35.3 beats/minute (control rate 279.2 beats/minute, cycle length 214.9 $\pm$ 7 msec, ventrolateral cardiac nerve stimulation rate 314.5 beats/minute, cycle length 190.8 $\pm$ 5.4 msec) ($p < 0.001$) (Figure 3). The AH interval at all paced rates was significantly shorter during ventrolateral cardiac nerve stimulation when compared to the control ($p < 0.01$) (Figure 4). Figure 5 demonstrates the effect of the ventrolateral cardiac nerve stimulation

compared to the control in a typical experiment. The AH interval at maximum paced rates was similar to control during ventrolateral cardiac nerve stimulation, (control 115.1 $\pm$ 5.2 msec, ventrolateral cardiac nerve stimulation 109.5 $\pm$ 5.8 msec) ($p = 0.25$) as seen in Figure 6.

The effective refractory period and the functional refractory period (group II) of the AV node were reduced during ventrolateral cardiac nerve stimulation by mean difference of 12 msec and 13.3 msec respectively ($p < 0.05$ for both) as seen in Figures 7 and 8 and Tables 1 and 2. Figure 9 is a graphic representation of data obtained during a single experiment and once again demonstrates the effect of sympathetic stimulation on conduction of premature atrial beats introduced at progressively more premature intervals. Figure 10 demonstrates the effect of ventrolateral cardiac nerve stimulation on conduction of the atrial extra stimulus.

Left Stellate Stimulation Compared to Ventrolateral Cardiac Nerve Stimulation

The paced maximum rate conducted 1:1 during left stellate stimulation and ventrolateral cardiac nerve stimulation, (group IA) were not statistically different from each other (cycle length for left stellate ganglion stimulation 118.9 $\pm$ 6.0 msec, ventrolateral cardiac nerve stimulation 191.7 $\pm$ 5.6 msec) ($p = 0.37$) as indicated in Figure 3. The ventrolateral cardiac nerve stimulation and left stellate

stimulation had similar and not statistically different (from each other) effects on the AH interval at paced rates (Figure 4).

As noted previously the AH intervals at the maximum conducted paced heart rates during left stellate stimulation and ventrolateral cardiac nerve stimulation were similar to each other as well as similar to the control value.

The effective refractory period and the functional refractory period of the AV node were effected similarly by left stellate ganglion stimulation and ventrolateral cardiac nerve stimulation and the effects were not statistically different. (Figures 7,8,9, and 10 and Tables 1 and 2)

Ventrolateral Cardiac Nerve Transection

The maximum heart rate conducted 1:1 after transection of the ventrolateral cardiac nerve (group IB) was not statistically different from that of intact non-stimulated controls (control 273.2 beats/minute, cycle 219 $\pm$ 9.8 msec, ventrolateral cardiac nerve transection 268.8 beats/minute, cycle length 223.2 $\pm$ 9.0 msec) ($p = 0.23$) (Figure 3). There were also no significant differences between AH intervals at any paced rate (Figure 11). Figure 12 is a representative tracing obtained showing this comparison. Furthermore, paced maximum rate during left stellate stimulation prior to ventrolateral cardiac nerve transection was markedly different from that following ventrolateral cardiac nerve transection.

FIGURE 11

AH Interval at Graded Pacing; Control, Ventrolateral Cardiac Nerve Transection and Left Stellate Ganglion Stimulation Following Ventrolateral Cardiac Nerve Transection

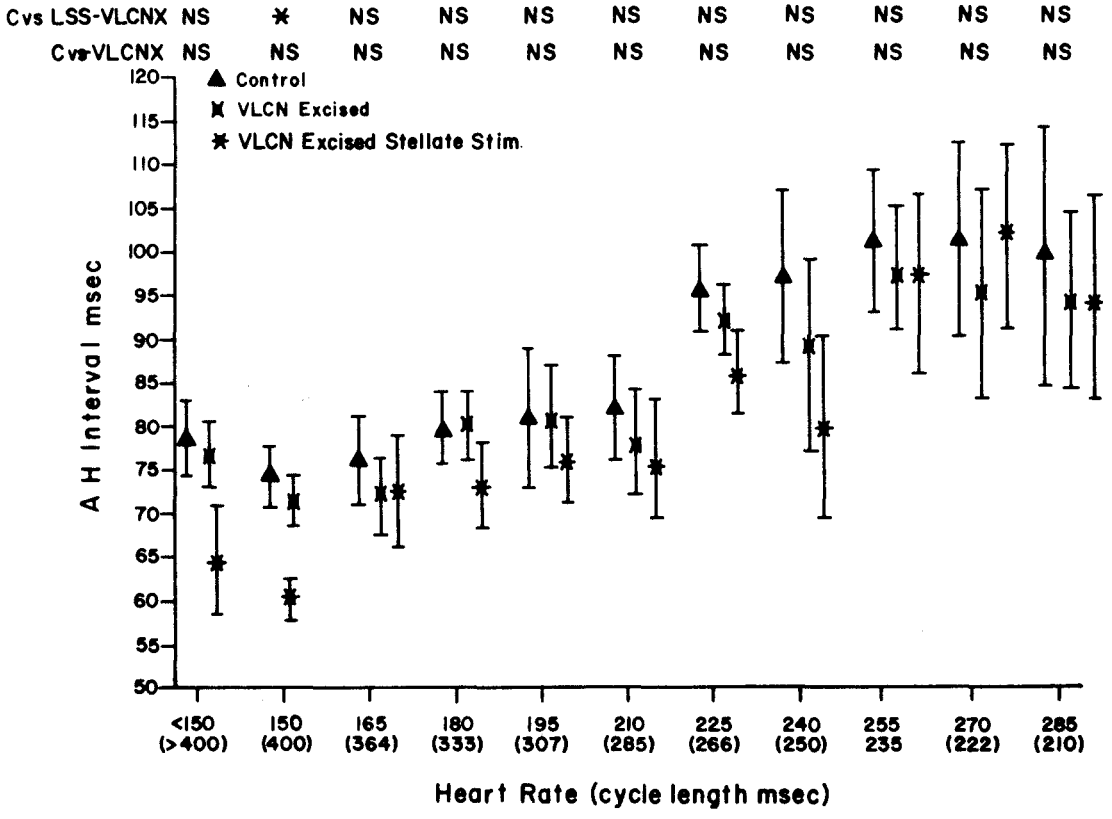

FIGURE 11

The results of ventrolateral cardiac nerve transection are shown and compared to the control and left stellate ganglion stimulation following ventrolateral cardiac nerve stimulation. The ordinate is the AH interval in msec. The abscissa is the graded pacing intervals from cycle length 400 to 210 msec. N - number of dogs for the various intervals are as follows: 400 N = 5, 400 N = 8, 364 N = 9, 333 N = 10, 307 N = 8, 285 N = 9, 266 N = 8, 250 N = 7, 235 N = 8, 222 N = 4, 210 N = 4. There is no statistical significance between the AH intervals at the various rates above 150/munute.

FIGURE 12

Recording During Control and Ventrolateral Cardiac Nerve Transection

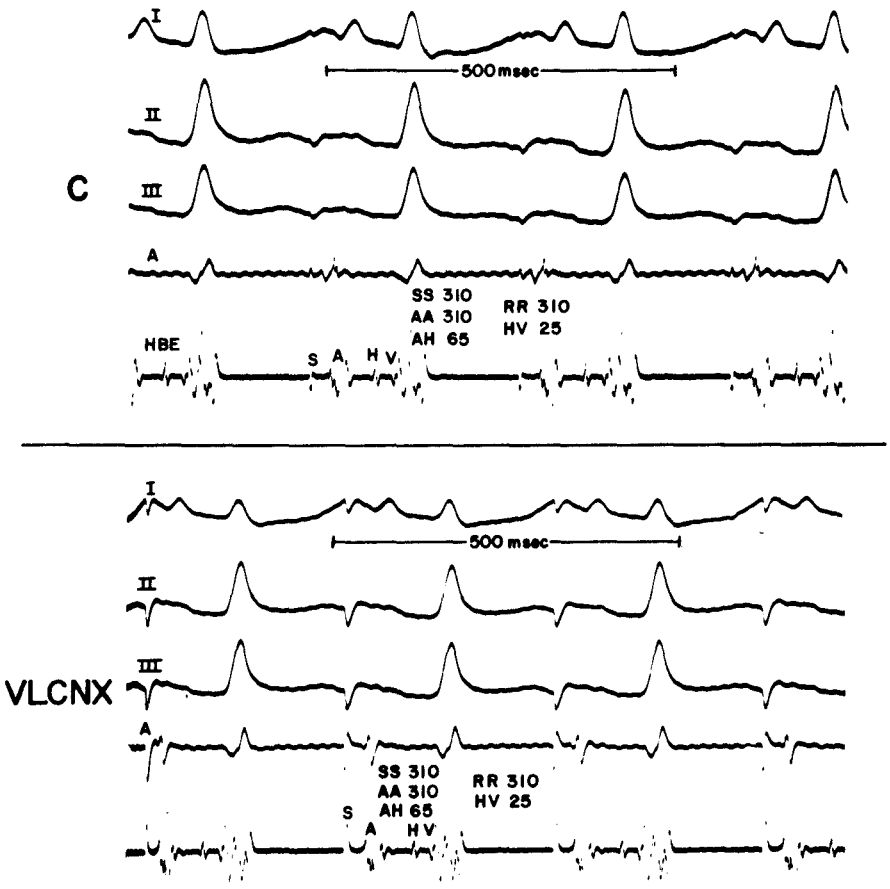

FIGURE 12

Recordings during control and ventrolateral cardiac nerve transection. Abbreviations are the same as in Figure 5. The AH interval during control is 65 msec and remains at 65 msec (bottom panel) after the ventrolateral cardiac nerve has been transected. Notice that all other intervals are also unchanged.

(Left stellate stimulation rate 305.8 beats/minute, cycle length 196.2 $\pm$ 9.9 msec, left stellate stimulation following ventrolateral cardiac nerve transection 279 beats/minute, cycle length 215.2 $\pm$ 6.5 msec) ($p = 0.01$) (Figure 3).

The AH intervals at graded paced rates after transection of the ventrolateral cardiac nerve, during left stellate stimulation, demonstrated variable effects which were not consistently different in either individual animals or when results were combined (Figure 13). The AH interval after transection of the ventrolateral cardiac nerve, during left stellate stimulation did not differ from intact unstimulated controls comparing heart rates above 150 beats/minute (cycle length 400 msec) (Figure 11).

FIGURE 13

AH Interval at Graded Pacing; Left Stellate Ganglion Stimulation and Left Stellate Ganglion Stimulation Following Ventrolateral Cardiac Nerve Transection

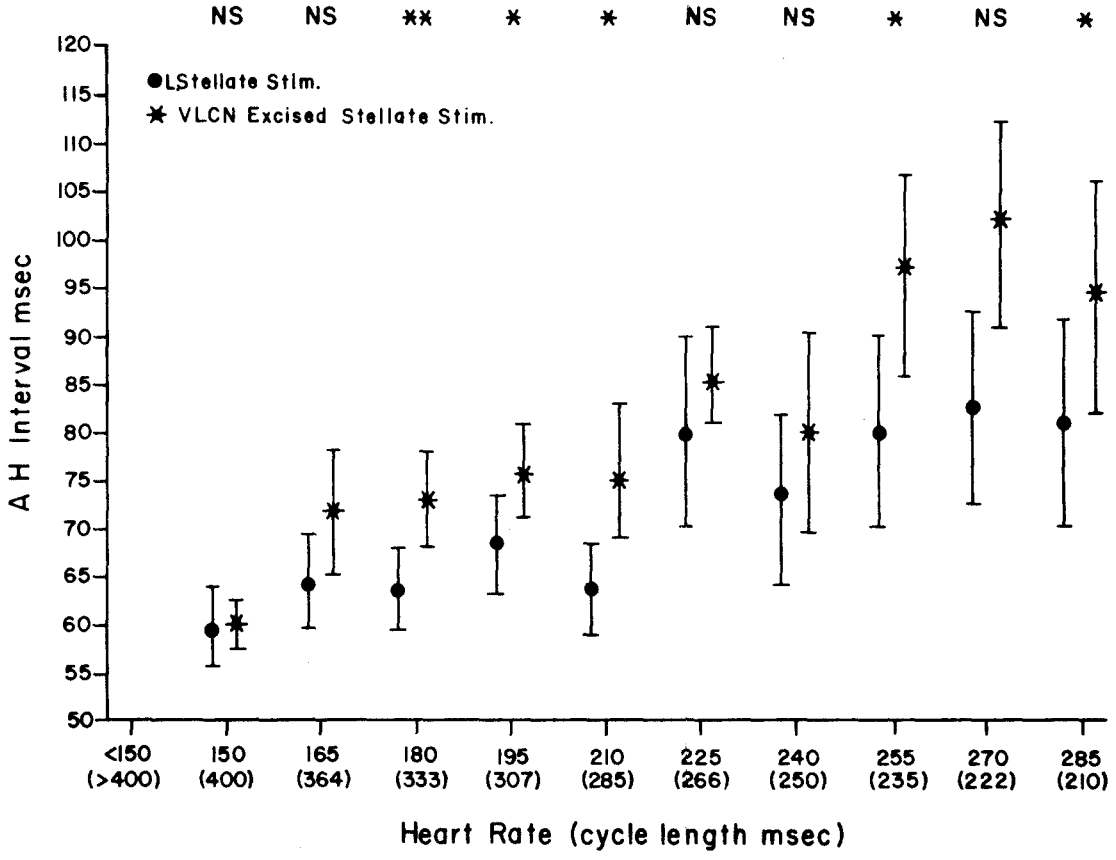

FIGURE 13

Comparison of left stellate ganglion stimulation prior to and following ventrolateral cardiac nerve transection. The ordinate shows the AH interval in msec. The abscissa, the heart rate N - number of dogs compared for each interval as follows: 400 msec N = 2, 364 msec N = 6, 333 msec N = 7, 307 msec N = 8, 285 msec N = 8, 266 msec N = 8, 250 msec N = 6, 235 N = 4, 222 msec N = 7, 210 msec N = 5. There is no trend noted in the statistical significance between the groups. AH intervals varied for each animal, as well as when means were compared for animals that were tested.

DISCUSSION

The effects of the left stellate ganglion activity through its subdivisions on AV nodal conduction and electrophysiology have not been systematically investigated. Mizeres[4] stimulated the ventrolateral cardiac nerve as part of his study to determine the pathways of cardiac aceleration. He did not quantitate the results of his study, nor did he compare responses to left stellate ganglion or ventrolateral cardiac nerve stimulation. Furthermore, Mizeres did not recognize the influence or the possibility of influencing AV conduction, and was only measuring heart rate.

Carlen and Katz[8] noted that in experimentally induced atrial fibrillation stellate ganglion stimulation enhanced AV conduction by increasing ventricular response rate to atrial fibrillation, but they did not compare left stellate ganglion stimulation to any other intrathoracic sympathetics. Sarnoff, et al.,[7] and Wallace and Sarnoff[8] stimulated the left stellate ganglion during part of their study. They quantitated the influence of left stellate stimulation upon the AH interval and inferred alterations on AV conduction, but they did not compare left stellate ganglion stimulation to changes in conduction elicited by excitation of the ventrolateral cardiac nerve.

Goldberg and Randall[16] noted the effect of left stel-

late stimulation upon AV conduction in animals during both paced and unpaced states. They quantitated their results but did not compare them to the ventrolateral cardiac nerve. Geiss, et al.,[5] demonstrated the functional anatomic relationship of the ventrolateral cardiac nerve to the AV node and Hagemen, et al.,[17] and Armour, et al.,[18] noted an effect of ventrolateral cardiac nerve stimulation on AV conduction but they did not compare results of ventrolateral cardiac nerve stimulation to responses to left stellate ganglion stimulation.

All of these previous studies suggested that left stellate ganglion stimulation and ventrolateral cardiac nerve stimulation may importantly serve to modulate AV nodal electrophysiologic function. The present experiments demonstrate for the first time and in a systematic fashion, the left sympathetic modulation of AV nodal conduction and refractoriness in the anesthetized, open-chested dog. Furthermore, the experimental results demonstrate the effect of left stellate ganglion stimulation is similar quantitatively on AV nodal conduction and refractoriness to those elicited by the ventrolateral cardiac nerve when stimulated (group II).

The maximum paced heart rate conducted before the onset of second degree block is nearly identical during ventrolateral cardiac nerve stimulation and left stellate ganglion stimulation (group IA). The maximum conducted paced

heart rate during stimulation achieved in this study are similar to those of Carlen and Katz,[8] and 10% less than those reported by Duchene-Marullaz[11]. This indicates that both the left stellate ganglion and the ventrolateral cardiac nerve have the same potential for enhancing AV nodal conduction. The decrease in AH interval compared to control at all paced heart rates prior to block is similar and equally reduced by either left stellate ganglion stimulation or ventrolateral cardiac nerve stimulation (Figures 3 and 4). This indicates that the ventrolateral cardiac nerve has the same potential for alteration of AV nodal conduction, as does the left stellate ganglion, and furthermore, that the ventrolateral cardiac nerve is the primary pathway from the left stellate ganglion to the AV node.

Wu, et al.,[26] have stated that the functional and effective refractory periods are more sensitive and reliable indicators of modulation of AV nodal conduction and function than maximum paced rates. Figures 7 and 8 demonstrate that left stellate ganglion stimulation and ventrolateral cardiac nerve stimulation yields statistically similar differences from control, each stimulation shifting the curves downward and to the left. There is no statistical difference between the effect of either ventrolateral cardiac nerve stimulation or left stellate ganglion stimulation on either the functional or the effective refractory period. The thesis protocol

which allows for comparison of interventions on maximum conducted heart rate as well as refractory periods eliminates the phenomena of "accomodation" described by Narula[33].

Additional information on the specific ventrolateral cardiac nerve effect upon AV nodal electrophysiology is demonstrated following transection of the ventrolateral cardiac nerve (group IB). Left stellate ganglion stimulation after ventrolateral cardiac nerve transection yields a slightly higher maximum paced heart rate compared to control. Yet, this proved not to be statistically different from the intact control preparation. The effect of left stellate ganglion stimulation after ventrolateral cardiac nerve transection on AH intervals during graded pacing is inconsistent when compared to intact left stellate ganglion stimulated dogs and not significantly different from control dogs. (Figures 11 and 13) Therefore, the ventrolateral cardiac nerve is a major pathway of left stellate modulation upon the electrophysiologic properties of AV node. Ventrolateral cardiac nerve transection in this anesthetized, open-chest preparation produced no effect on either maximum paced heart rate or AH interval during pacing. This indicates in this experimental preparation there is little significant resting influence on the AV node from the left stellate ganglion. Alternately, this loss of input may be simultaneously compensated by other sympathetic innervation such as the right-sided sympathetics[34],

elevated leves of catecholamines, or central nervous system pathways.

The autonomic nervous system, specifically the left stellate ganglion and the ventrolateral cardiac nerve have been demonstrated in this thesis to have profound effects on the functional refractory period and the effective refractory period of the AV node. At present it is only possible to hypothesize what the specific alterations in electrophysiologic properties may mean. However, it is possible to hypothesize that the combination of right stellate ganglion stimulation[35] which increases rate of firing by the sinus node may in fact be coordinated with the effects of left stellate ganglion stimulation upon conduction of the increased rate of impulse traffic across the AV junctional regions. If this were not the case, increase in heart rate caused by increase in impulse formation would result in block at the AV node[1].

Sarnoff, et al.,[7] and Wallace and Sarnoff.,[6] speculated that enhancement in AV conduction may be a "necessary" phenomenon in order to ensure maximum benefit of the increased heart rate seen during catecholamine administration.

It is much more attractive to postulate that alterations in AV nodal conduction which occur with left stellate stimulation or ventrolateral cardiac nerve stimulation may be related to phenomena associated with arrhythmia. AV junctional tachycardias as described by Coumel and Berold[36] and Wu[37] are most likely due to a reentrant tachycardia which

involves alterations in refractoriness of two parallel pathways, one or both of which may involve the AV node. Janse, et al.,[38] have speculated that the delay in AV nodal transmission takes place in the AN zone and that during normal conduction this delay accounts for the greater part of the total AV nodal delay. It remains now for microelectrophysiologists to determine if left stellate ganglion stimulation and ventrolateral cardiac nerve stimulation effect the conduction through the AV node at this level.

Alterations in functional and effective refractory periods of the AV node by left stellate stimulation and ventrolateral cardiac nerve stimulation demonstrate important dromotropic effects. During control periods and during all interventions the longest AH interval remained the same, indicating that it is the recovery of function (i.e. recovery from a refractoriness that allows greater heart rates to be conducted through the AV node.) It is not a combination of greater conduction speed and the capability of conducting over a longer period of time, but solely a property of enhanced recovery of function and greater rate of conduction that allows for the greater heart rate to be conducted.

SUMMARY AND CONCLUSIONS

In summary, the experiments and the data presented here have demonstrated the following:

1. The maximum heart rate conducted 1:1 is similar during left stellate ganglion stimulation and ventrolateral cardiac nerve stimulation and is markedly greater than during control, nonstimulation periods (group IA).

2. Transection of the ventrolateral cardiac nerve, does not effect the maximum conducted heart rate in unstimulated animals, but eliminates the effect of left stellate ganglion stimulation on maximum conducted heart rate (group IB).

3. Left stellate ganglion stimulation and ventrolateral cardiac nerve stimulation markedly decrease the effective and functional refractory periods of the AV node. The degree of shortening is similar during both stimulations (group II).

4. Left stellate ganglion stimulation and ventrolateral cardiac nerve stimulation markedly reduced AH intervals and therefore conduction time through the AV node, at heart rates from 150 to 285 per minute. The degree of shortening in AH interval is similar for both stimulations (group IA).

5. The AH interval for maximum conducted heart rates, is similar for control, left stellate ganglion stimulation, ventrolateral cardiac nerve stimulation, ventrolateral cardiac nerve transection and ventrolateral cardiac nerve transection

during stellate stimulation (groups IA and IB).

6. The AH interval after transection of the ventrolateral cardiac nerve, at heart rates between 150 and 300 per minute, remained unaffected by left stellate ganglion stimulation (group IB).

7. The ventrolateral cardiac nerve is a major pathway for left stellate ganglion effects on AV nodal conduction properties and refractory periods.

BIBLIOGRAPHY

1. Hoffman, B.J. and Cranefield, P.F.: Electrophysiology of the heart. Futura Publishing Co. Inc., Mount Kisco, New York, p 133, 1976.

2. Nonidez, Jose F.: Studies on the innervation of the heart. I. Distribution of the cardiac nerves with special reference to the identification of the sympathetic and parasympathetic post ganglionics. Am. J. Anat. 65:361-413, 1939.

3. Mizeres, Nicholas J: The anatomy of the autonomic nervous system in the dog. Am. J. Anat. 96:285-318, 1955.

4. Mizeres, Nicholas J.: The origin and course of the cardioaccelerator fibers in the dog. Anat. Rec. 132:261-279, 1958.

5. Geiss, W.P., Kaye, M.P. and Randall, W.C.: Major autonomic pathways to the atria and SA and AV nodes of the canine heart. Am. J. Physiol. 224:202-208, 1973.

6. Wallace, A.G. and Sarnoff, S.J.: Effects of cardiac sympathetic nerve stimulation on conduction in the heart. Cir. Res. 14:86-92, 1964.

7. Sarnoff, S.J., Gilmore, J.P. and Wallace, A.G.: The influence of autonomic nerve activity on the adaptive mechanisms in the heart. In Nervous Control of the Heart (Randall, W.C. ed.) Williams and Wilkins, Baltimore, pp 54-129, 1965.

8. Carlen, S.A. and Katz, L.N.: The ventricular rate in faradically maintained auricular fibrillation: An index of AV conductivity. Am. J. Physiol. 127: 272-280, 1939.

9. Arnould, P., Duchene-Marullaz, P., Boulange, M., Schaff, G.: Le tonus dromotrope des nerfs extrinseques du coeur chez le chien. C.R. Soc. Biol. (Paris) 5:1069-1071, 1963.

10. Duchene-Marullaz, P., Arnould, P., Schaff, G., Lavarenne, J., Billaud, J.: Comparaison des effets chronotrope, inotrope et dromotrope de l'excitation du stellaire droit chez le chien chloralose. J. C.R. Biol (Pairs) 160:1589-1589, 1966.

11. Duchene-Marullaz, P., Lavarenne, J., Schaff, G., Lautier, F.: Comparaison des effects sur la conduction auriculo- ventriculaire de la stimulation des ganglions stellaires droit et gauche. C.R. Soc. Biol. (Paris) 162:426-428, 1968.

12. Levy, M.N. and Zieske, H.: Autonomic control of cardiac pacemaker activity on atrioventricular transmission. Appl. Physiol. 27:465-570, 1969.

13. Irisawa, H., Caldwell, W.M., Wilson, M.F.: Neural regulation of atrioventricular conduction. Jap. J. Physiol. 21:15-25, 1971.

14. Priola, D.V.: Effects of beta receptor stimulation and blockade on AV nodal and bunch branch conduction in the canine heart. Am. J. Cardiol. 31: 35-40, 1973.

15. Spear, J.F. and Moore, E.N.: Influence of brief vagal and stellate nerve stimulation on pacemaker activity and conduction within atrial ventricular conduction system of the dog. Cir. Res. 32:27-41, 1973.

16. Goldberg, J.M. and Randall, W.C.: Dromotropic effects of stellate stimulation on the AV node and internodal pathways. Proc. Soc. Exp. Biol. and Med. 143:623-628, 1973.

17. Armour, J.A., Hageman, G.R. and Randall, W.C.: Arrhythmias induced by local cardiac nerve stimulation. Am. J. Physiol. 223:1068-1075, 1972.

18. Hageman, G.R., Goldberg, J.M., Armour, J.A., Randall, W.C.: Cardiac dysrhythmias induced by autonomic nerve stimulation. Am. J. Cardiol. 32:823-830, 1973.

19. Scherlag, B.J., Helfant, R.H., Damato, A.N.: A catheterization technique for His bundle stimulation and recording in the intact dog. J. Appl. Physiol. 25:425-428, 1968.

20. Scherlag, B.J., Kosawsky, B.D. and Damato, A.N.: A technique for ventricular pacing from the His bundle of the intact heart. J. Appl. Physiol. 22:584-587-, 1967.

21. Scherlag, B.J., Lau, S.H., Helfant, R.H., Berkowitz, W.D., Stein, E. and Damato, A.N.: Catheter technique for recording His bundle activity in man. Circ. 39:13-18, 1969.

22. Scherlag, B.J., Samet, P., Helfant, R.H.: His bundle electrogram: A critical appraisal of its uses and limitations. Circ. 46:601-613, 1972.

23. Scherlag, B.J., Abelleira, J.L. and Samet, P.: Electrode catheter recordings from the His bundle and left bundle in the intact dog. In Research in Physiology (ed. Kao, F.F., Koizumi, K. and Vassale, M.) Aulo Gaggi, Bologna, pp 223-238, 1973.

24. Narula, O.S.: Validation of His bundle recording: Limitation of catheter technique. In His Bundle Electrocardiography and Clinical Electrophysiology. (ed. Narula, O.S.) F.A. Davis and Company, Philadelphia, pp 65-91, 1975.

25. Reddy, C., Pratap, Damato, A.N., Akhtar, Masood, Ocunkelu, Bimbola, J., Caracta, A.R., Ruskin, J.N., Lau, S.H.: Time dependent changes in the functional properties of the atrioventricular conduction system in man. Circ. 52:1012-1022, 1975.

26. Wu, D., Denes, Pablo, Rosen, K.M.: Refractoriness of atrioventricular conduction. In His Bundle Electrocardiography and Clinical Electrophysiology. (ed. Narula, O.S.) F.A. Davis and Company, Philadelphia, pp 95-103, 1975.

27. Mendez, C., Gruhzit, C.C. and Noe, G.K.: Influence of cycle length upon refractory period of auricles, ventricles and the AV node in the dog. Am. J. Physiol. 184:287, 1956.

28. Balis, G., Monroe, R.: The pharmacology of chloralose: A Review. Psycholparmacologia 6:1-30, 1964.

29. Urthaler, F., Krames, B.L. and James, T.N.: Selective effects of pentobarbital on automaticity and conduction in the intact canine heart. Cardio. Res. 8:46-57, 1974.

30. Peiss, C.M., Manning J.W.: Effects of sodium pentobarbital on automaticity and conduction in the intact canine heart. Circ. Res. 14:228-235, 1964.

31. Armour, J.A. and Randall, W.C. Functional anatomy of canine cardiac nerves. Acta Anatomica, 91:510-528, 1975.

32. Bahn, A.K: Difference between correlated sample means (Paired Data). In Basic Medical Statistics Grune and Stratton Inc. New York pp 144-156, 1972

33. Narula, O.S., Runge, M.: Accommodation of AV nodal conduction and fatigue phenomenon in the His Purkinje System. In The Conduction System of the Heart (ed. Wellens, H.J.J., Lie, K.I., Janse, M.J.) Lea and Febiger, Philadelphia, 296-315, 1976

34. Fishman, D.L., Moran, J.F., Randall, W.C., and Gunnar, R.M.: Sympathetic modulation of canine AV nodal conduction properties. Circ. (Suppl. III) 56:81, 1977.

35. Randall, Walter, C. Sympathetic control of the heart, In Neural Regulation of the Heart (ed. Randall, W.C.) Oxford University Press, New York, pp 55-60, 1977.

36. Coumel, P.H., Barold, S.S.: Mechanisms of supraventricular tachycardia. In His Bundle Electrocardiography and Clinical Electrophysiology. (ed. Narula, O.S.) F.A. Davis and Company, Philadelphia, pp 65-91, 1975.

37. Wu, D., Denes, P., Rosen K.M: Refractoriness of atrioventricular conduction. In His Bundle Electrocardiography and Clinical Electrophysiology. (ed. Narula, O.S.) F.A. Davis and Company, Philadelphia, pp 99-103, 1975.

38. Janse, Michiel, J., Van Capell, Frans J.L., Anderson, Robert H., Touboul, Paul, Billetle, Jacques: Electrophysiology of the atrioventricular node of the isolated rabbit heart. In The Conduction System of the Heart (ed. Wellens, H.J.J., Lie, K.I., Janse, M.J.) Lea and Febiger, Philadelphia, pp 296-315, 1976.

APPROVAL SHEET

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The thesis is therefore accepted in partial fulfillment of the requirements for the degree of Master of Science.

April 18, 1978
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