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Evidence for Shifting Supraventricular Pacemakers During Sympathetic Stimulation Before and After SA Node Excision

John M. Geesbreght
Loyola University Chicago

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EVIDENCE FOR SHIFTING SUPRAVENTRICULAR PACEMAKERS
DURING SYMPATHETIC STIMULATION BEFORE
AND AFTER SA NODE EXCISION

by
John M. Geesbreght

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

June
1970

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ACKNOWLEDGMENTS

Dr. Walter C. Randall has provided the rare combination of a truly academic atmosphere and an environment of enthusiastic understanding for the needs of this student of research. His devotion and sensitivity to the field of physiology specifically, and to experimental biology generally, has had an immeasurable impact upon my attitudes as well as my scientific knowledge.

I thank him for his assistance in preparing this manuscript, but more, I thank him for the close association, and the opportunity to work under his supervision.

I extend my appreciation to Dr. Philip Dobrin, whose ready confidence and helpful criticism has contributed substantially to my graduate education.

For Mary Lee, my wife, who provided continual encouragement and understanding, I am deeply grateful.
BIOGRAPHY

John Michael Geesbreght was born on April 29, 1944 in Chicago, Illinois. After graduation from elementary school in 1958 he attended Foreman High School until June of 1962. In the fall of that year he was accepted in the Chicago Undergraduate Division of the University of Illinois in the pre-medical curriculum.

Mr. Geesbreght was enrolled in the 1965 freshman class of the Loyola University, Stritch School of Medicine. During the final quarter of his senior year, he entered the Graduate School of Loyola University under the guidance of Walter C. Randall, Professor and Chairman in the Department of Physiology. Postponing medical school graduation for one year until July of 1970 Mr. Geesbreght became a full-time graduate student, seeking a degree of Master of Science.

In April of 1970, he co-authored a paper on the effects of small nerve stimulation upon cardiac pacemaker activity given to the Federation of American Societies for Experimental Biologist, in Atlantic City, New Jersey. During that same month he presented his research on shifting cardiac pacemakers before and after SA nodal excision at the Student American Medical Association - University of Texas Research Forum, in Galveston, Texas.
LIST OF PUBLICATIONS


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CHAPTER I

INTRODUCTION

The SA node is generally acknowledged to be the 'normal' pacemaker of the heart. If initial depolarization takes place outside the SA nodal region, such a focus is usually termed 'ectopic.' This terminology is used to denote its singular location, but perhaps more importantly to connote an inferior capacity to institute electrical events in the cardiac cycle. However, recent evidence suggests that there are spontaneous changes in the origin of atrial wave fronts, contradicting the concept of a single physiologic pacemaker. Also, when atrial depolarization is initiated, the propagation of the excitatory wave front is thought to coincide with one of two basic proposals:

1. radial transmission over the atria
2. preferential conduction along specific pathways

Questions concerning the mechanisms of atrial depolarization and pacemaker activity were thought to be part of a broader topic, that of local supraventricular excitability. It was with this in mind that the following experimental questions were proposed:

1. What is the role of non-nodal pacemaker activity on the spontaneously beating heart?
2. What changes in pacemaker activity could be induced by extrinsic nerve stimulation?

3. What effect would surgical excision of the SA node have on non-nodal pacemaker function and responsiveness of the heart to sympathetic nerve stimulation?
A. HISTORICAL REVIEW OF PACEMAKER ACTIVITY. Anatomic and physiologic evidence implicating a site near the junction of the superior vena cava and right auricular appendage, as a cardiac pacemaker, was introduced in 1907 by Keith and Flack. Wybauw (1910) used an Einthoven thread galvanometer to localize the point of pacemaker activity by the determination of the first electrical negativity manifested in the supraventricular region. Results corresponded to the anatomic description of Keith and Flack. Later, Flack proposed that the Sino-Auricular Node (SA node) was the dominating source of rhythm in the heart (Flack, 1910). He also reported changes in heart rate resulting from electrical stimulation of stellate and vagal nerves. It was further noted that stimulation of the right-sided nerves produced greater heart rate alterations than did similar procedures on the left.

To confirm his findings, the entire region of the SA node was clamped, the heart was then stimulated through extrinsic nerves as before, and changes in heart rate noted. He found a considerable diminution in responsiveness of the heart to these stimulations and therefore concluded that the stimulation effects were a result of the neural activity on the SA node.
Of interest is the fact that these early investigators were aware of the existence of non-SA nodal pacemaker activity. In fact, their recordings of initial depolarization at the region of the coronary sinus led to the characterization of the term, coronary sinus rhythm. Experimentation continued on the origin of the heart's electrical activity (Lewis, 1910; Erlanger, 1907) until the concept of 'normal sinus rhythm' was introduced in 1914 by Eyster and Meek. Thus it appeared that the 'dominating' nature of Keith and Flack's node was now to be known as the 'normal' or physiologic pacemaker of the heart. Such a concept was solidly propagated in the literature despite repeated evidence indicting non-SA nodal areas with pacemaker ability (Erlanger, 1910) (Meek and Eyster, 1914a) (Meek and Eyster, 1914b) (Eccles and Hoff, 1934) (Barker, et al, 1920). Studies by Erlanger as early as 1907 attributed spontaneous rhythmicity to areas of the inter-atrial septum, coronary sinus and in rare circumstances to the left atrium.

The idea of normal nodal rhythms was also fostered by a description by Lohmann (1904) of A-V nodal rhythm seen after ablation of the SA node. Clinical evidence was also introduced to show A-V nodal rhythm in humans (Mackenzie, 1904). A positive correlation between the two anatomical nodal structures and physiologic pacemaker activity was, to the exclusion of non-nodal areas, then generally accepted by the scientific community (Puech, 1916) (Lewis, 1925) (Eyster and Meek, 1921).

B. ATRIAL ACTIVATION. With the isolation of the 'normal' anatomic position for the cardiac pacemaker, the next logical step was to investigate wave propagation from this point. In 1914 Lewis and co-workers introduced
evidence for the radial spread of atrial depolarization. They believed that once initial activity had commenced at the SA node, activation of the surrounding musculature was accomplished by depolarizing an ever increasing circle about the node. The proponents of this concept are many (Puech, et al, 1954) (Abildskov, et al, 1955) and have commanded the majority thinking on this subject for over half a century (Ruch and Patton, 1965) (Mountcastle, 1968).

However, as far back as 1916 another group having a different opinion was stating their views. Eyster and Meek were among the first to propose asymmetrical spread through the atria. This fact served to drive the followers of Lewis and those of Eyster into two camps. Eyster could not reconcile a uniform radial propagation with observations that the impulse reached the A-V node before it reached all the muscular tissue in the body of the right atrium. Also, why would atrial-ventricular dissociation occur after discrete lesions were made in the vicinity of the SA node which left considerable atrial muscle intact (Eyster and Meek, 1916).

Momentum for the preferential conduction group was gained when in 1916 Bachman demonstrated the existence of an interatrial band (Bachman's bundle). Its role in the activation of the left atrium was clearly demonstrated by Bachman himself when he preferentially crushed this pathway, resulting in an increased dissociation between depolarization of the right and left atria. Confirmation of the significance of this interatrial band (Rothberger, et al, 1927) (Matsuoka, 1957) was made by ligating the artery which supplies Bachman's bundle. No change was seen in interatrial con-
duction if other areas were similarly treated (Condorelli, 1929).

Though the presence and apparent function of a preferential conductile band was demonstrated, it was still believed generally that this band was just a muscular connection providing a direct route to the left atrium. Then in 1931, Taussig and in 1932, Todd identified histologically, Purkinje-like fibers within the atria. Paes de Carvalho et al, (1961) while studying atrial depolarization, noted that some areas of muscular tissue seemed to be activated by a wave front originating near the crista terminalis. He also made intracellular recordings of Purkinje-like potentials from selected areas of the right atrium.

Localization of Purkinje-type fibers to specific tracts within the atrium was accomplished by Robb and Petri (1961) in monkey embryos. They described two internodal tracts and Bachman's bundle both grossly and histologically.

A unified, anatomical picture of atrioventricular conductile tissue was finally achieved when the internodal pathways were described by James (1963) in human hearts. Radiating from the SA node (James, 1961) (Truex, 1967a) like spokes on a wheel, the three internodal pathways, anterior, middle and posterior, course through the free wall of the right atrium and interatrial septum until they terminate at the AV node (Truex and Smythe, 1967).

The embryologic development of these pathways has recently been described (James, 1970). They are said to traverse segments which are a residuum of the primitive sinus venosus. The cells of the tracks are a
mixture of Purkinje cells and cells resembling contractile myocardium. These pathways are distinguishable anatomically from the rest of the musculature, not by a sheath, but by the interposition of a region of tissue largely composed of fat and collagen.

Conduction speed has been measured in acute dog experiments for the anterior internodal pathway and was found to be distinctly more rapid than that of atrial muscle, but not as rapid as that of the ventricular Purkinje system (Wagner, et al, 1966). Increased conduction velocities through the region of the pathways has been confirmed in isolated rabbit heart (Sano and Yamagishi, 1965).

Evidence of the supernormal excitability of Bachman's bundle, as compared to atrial muscle cells, was reported by Childers et al (1968). They further showed that these specialized cells were more responsive to the effects of extrinsic nerve stimulation than muscle tissue. Vagal stimulation increased interatrial conduction time and decreased the supranormal enhancement of conduction velocity.

One possible role of the internodal tracts in the excitation of ventricular myocardial structures was shown by Janse (1969). Through artificial pacing from each of the three internodal pathways he demonstrated differences in A-V nodal conduction and refractoriness. These differences were dependent upon the direction from which the A-V node was depolarized. Pacing from the anterior tract produced in the A-V node a decrease in amplitude, rate of rise and duration of the action potential. The configuration was also modified to include a hump in the wave form. Posterior
internodal pacing was associated with A-V nodal activity not unlike that seen in the control state.

These studies suggest the possibility of an extrinsic nervous mechanism which could mediate changes in atrial excitability, and therefore conduction in these specialized atrial fibers, which in turn could influence refractoriness of the A-V node itself.

C. CURRENT CONCEPTS. The relative roles of the sympathetic and parasympathetic activity on inotropism (Randall, et al, 1969) and chronotropism (Warner and Russel, 1966) (Glick and Braunwald, 1965) have been studied for many years. Their antagonistic effects on cardiac performance is well known (Ruch and Patton). However, knowledge of changes in origin and direction of conduction (dromotropic effect), influenced by the autonomic nerves, is scant. Ueda and co-workers, (1964) recording vector electrocardiograms, noted the differential effects on wave front direction with right and left stellate stimulation. He hypothesized that differences in regional innervation may, in part, explain his findings.

Recently the work of Bowman et al (1968) has dramatically demonstrated vagal induced pacemaker shifts within the SA node using microelectrode techniques. This study points out the capacity of the parasympathetics to modify pacemaker location through local changes in excitability. Other observations of changes in atrial depolarization both experimentally (Priola and Randall, 1964) and clinically (Mirowski, et al, 1966) have been based on electrocardiographic criteria alone. Brody and Woolsey (1967) continuously monitored the ECG traces of 71 normal subjects and found that 41
showed sustained periods of ectopic atrial beating. They concluded that this high incidence of variability indicated that shifts of pacemaker location, variable exit sites from the SA node, and preferential conduction pathways might be implicated as causes for these spontaneous electrocardiographic changes.
CHAPTER III

MATERIALS AND METHODS

A. SURGICAL AND STIMULATION PROCEDURES. Acute experiments were performed on 26 open-chest mongrel dogs of 15-20 Kg weight. Anesthesia was maintained with Sernylan (2 mg/Kg) I.M. and Chloralose (80 mg/Kg) I.V., throughout the surgical procedures. Respiration was accomplished through an automatic cycling, positive pressure respirator. Compressed air was delivered to the animal through a tracheotomy tube. A thermostatically controlled, water heating pad was used to maintain body temperature.

The chest was opened by cautery at the third intercostal space transsternally. Both cervical vagosympathetic trunks and stellate ganglia were isolated and totally decentralized for efferent stimulation (Miller, 1964).

Seven unipolar electrodes and lead II of an Electrocardiogram (Marriott, 1962) were employed. Placement of the unipolar leads is illustrated in Figure 1. Right atrial (RA), left atrial (LA), anterior internodal (AIN), and right ventricular (RV) leads were positioned epicardially, while middle internodal (MIN), posterior internodal (PIN), and HIS bundle (HIS) electrodes were inserted endocardially. Inflow occlusion technique was utilized to
Right superior-lateral view of heart showing placement of the seven unipolar electrodes.
implant the intracardiac electrodes. The azygous vein was ligated while
umbilical tape snares were looped around the superior vena cava (SVC) and
inferior vena cava (IVC), care being taken to preserve nerve pathways along
the SVC (Kaye, et al, 1970). A large Statinsky clamp was used to clamp the
lateral aspect of the auricular appendage and free wall of the right atrium.
Then a 2.5 cm incision was made in the clamped tissue, avoiding the inter-
nodal conduction pathways, and 5-0 Ethiflex guide sutures were sewn at both-
ends of the incision. After a period of forced hyperventilation, the cavae
were occluded, atrial contents aspirated and the three electrodes implanted.
The incision was clamped and the cavae were gradually released so as not to
produce dilatation of myocardium. When the incision was closed, the clamp
was removed and respiration returned to its control state. At no time did
the restriction of caval flow amount to more than sixty seconds.

Conduction pathway electrodes were positioned according to the
anatomical description provided by James (1963). The RA lead was attached
to the right atrium in the SA node, at the superior junction of the SVC
and the auricular appendage. The AIN pathway, the middle segment of which
is also known as Bachman's bundle, leaves the SA node to travel anterior to
the SVC. It then courses along the superior portion of the interatrial
septum (IAS) where it bends to travel caudad in the IAS to its termination
at the superior margin of the A-V node. Electrode AIN was inserted across
this pathway at the superior margin of the IAS.

The MIN and PIN tracts leave the SA node jointly to travel in the
superior segment of the crista terminalis. The two tracts then divide,
leaving the PIN alone to follow the crista caudally. At its caudal aspect, the PIN then courses medially and inferiorly to the coronary sinus at the eustachian ridge and connects with the AV node on its lateral margin. Lead PIN was hooked into the eustachian ridge. After the MIN leaves the crista, it courses dorsally to the cavae to the limbus of the fossa ovalis. It then angles posteriorly to terminate at the A-V node just lateral to the fibers of the AIN tract. The limbus was impaled with the MIN lead.

Electrode HIS, reflecting electrical activity in the basal portion of the interventricular septum, was placed in the area of the HIS bundle just medially to the septal leaflet of the tricuspid valve. The LA lead was inserted into the medial surface of the auricular appendage close to its junction with the lateral free wall, while RV activity was recorded from the epicardial surface of the sinus region. All intracardial electrodes were barbed to insure secure placement.

In 12 preparations, after control, right and left stellate stimulation data were recorded, the SA node was surgically excised. An Allis forcep was used to grasp the superior-lateral junction of the SVC and RA. A small Statinsky clamp was then positioned around the Allis to isolate a segment of tissue approximately 2 X 2 cm. The tissue within the clamp was then excised and sent for histologic sectioning. The RA electrode was reimplanted adjacent to the incision and the stimulation procedure repeated.

Stimulations were performed on the decentralized stellate ganglia using a Grass model 5-S stimulator at frequency, duration, and voltage of 10Hz., 5 msec., and 5 volts. These parameters were monitored on a cathode
ray oscilloscope to insure supramaximal stimulation throughout all experiments.

B. RECORDING AND MEASUREMENT TECHNIQUE. Unipolar leads were chosen because of the ease with which they could be inserted during the inflow occlusion procedure. It has been repeatedly shown that for purposes of area localization of depolarization activity, bipolar and unipolar leads record identical data (Melbin, et al, 1969) (Spach, et al, 1969).

Recordings were made simultaneously on a model 7 Grass polygraph and a Precision Instrument, model 6100, eight channel FM electromagnetic tape recorder. Data were also displayed on an eight channel cathode ray oscilloscope used for playback purposes.

Advantage was taken of the differential speed capabilities of the FM tape recorder to achieve time-scale expansion of the data (Brophy, 1966). Tape speed of 3.75 ips at 1,000 Hz. frequency response was used in the acquisition of records while playback speed was reduced to 0.375 ips at 100 Hz. With the paper drive at 100 mm/sec. playback into the driver amplifiers resulted in a ten fold expansion of the time-scale. This procedure made possible the interval measurements (in msec) needed in this study.

All driver amplifiers were set to reproduce 1000 Hz. Both high frequency (1000 Hz) and low frequency (40 Hz) preamplification was used on alternate and during single experiments and found not to effect the results. Pen frequency response was tested with a Wavetec generator and was found to allow reproduction of 45 Hz. sine waves without attenuation.

Ordinates are shown in each supraventricular channel to emphasize
points where local depolarization activity commences. These points coincide with the onset of the steepest rate of rise and are used in making sequence measurements. Secondary deflections in the supraventricular leads are probably due to volume conduction reflecting the massive ventricular depolarization.
CHAPTER IV

EXPERIMENTAL RESULTS

A. THE EFFECTS OF RIGHT AND LEFT STELLATE STIMULATION ON PACEMAKER SHIFTING AND ATRIAL ACTIVATION. Two types of measurements were made. First, the initial site of electrical activation was determined, as detected from the electrogram traces. Comparisons were made of the changes in the site of initial activity and electrocardiographic traces as related to P-R interval and P-wave configuration. Findings due to right stellate stimulation were contrasted with those elicited by left stellate stimulation. Left stellate stimulation resulted in the most varied distribution of initial electrogram activity.

The most frequent site for initial detection of atrial depolarization, during left sympathetic stimulation, was at the PIN electrode (coronary sinus rhythm). The next most frequent sites in a descending order of occurrence were: SA node, AV node (as judged by simultaneous activation of atria and ventricles with absence of P-wave and normal QRS), and at the superior border of the interatrial septum (AIN lead). With only rare exceptions, right stellate stimulation was associated with precedence of
Comparison of two SA nodal rhythms (A & B) and a left atrial rhythm (C). SA nodal rhythm cycles are shown as recorded directly from the polygraph. This is contrasted to SA nodal and left atrial rhythm records obtained after time-scale expansion.
the SA node.

Secondly, the electrographic activation sequences following the initial deflection, frequently shifted independently. For example, with the pacemaker in the SA node, the sequence in the control state often consisted of AIN--PIN--MIN--LA. During right stellate stimulation a sinus rhythm was maintained but the pattern of internodal pathway excitation frequently changed to AIN--MIN--PIN--LA. Thus, a changing sequence of excitation with a fixed pacemaker site was commonly observed. This most often characterized the response to right stellate stimulation. Further, the pacemaker site was localized to the SA nodal region in 93% of right stellate stimulations.

In marked contrast, electrical excitation of the left stellate ganglion very often resulted in both changing initial site of depolarization (only 31% in SA node) and activation pattern at the internodal pathway electrodes. Because of the undetermined distances and conduction velocities involved, with the placement of these supraventricular electrodes, no positive statement of wave front direction can be made other than there was change relative to the control pattern of action potential spread.

Comparisons between the traces as recorded at 100 mm/sec directly on the polygraph (figure 2A) and the tape playback at 1000 mm/sec (2B and C) illustrate the recording procedures employed. The pattern of a regular supraventricular rhythm at a heart rate of 130/min., with initial electrical activity in the superior lateral portion of right atrium (SA node) is shown with the expected P and QRS wave configurations in the ECG.

Sequential activation progressed from the SA node region through
FIGURE 3

RIGHT STELLATE STIMULATION

A  B  C  D  E
RA
AIN
MIN
PIN
LA
HIS
ECG
RV

Five of ten successive cycles showing pacemaker location shifting from a site in, or near the posterior internodal pathway to the region of the SA node. Continuous right stellate stimulation beginning four seconds prior to the cycle depicted in panel A.
the internodal pathways to left atrial and HIS bundle areas, and lastly to the epicardial surface of the right ventricular sinus. This right atrial rhythm (panel B) is contrasted with one in which the initial depolarization was observed to occur spontaneously at the left atrial lead (panel C) only a few cycles later. A prominent shift in all five supraventricular recordings occurred while HIS-ventricular configurations remained unaltered. Electrical activity first appeared in the left atrial lead, followed by the internodal pathways and still later by right atrial activity. P-wave configuration became so depressed and biphasic as not to allow a P-R interval measurement.

Figure 3 shows five alternate cardiac cycles representing a period of ten successive beats in which the pacemaker shifted from a site in, or near the posterior internodal pathway to the superior-lateral region of the right atrium, presumably the SA node. The first cycle (panel A) indicates the excitation wave was initiated in or around an internodal pathway site, from which it spread throughout the atria, arriving at the RA and LA leads almost simultaneously. The P-wave of the ECG was of low amplitude though its temporal relationships were within normal limits. Electrical stimulation of the right stellate ganglion had been initiated four seconds prior to the cycle depicted in panel A, and was continuous throughout the entire period encompassed by the figure. The configuration illustrated in panel A was identical to that in control cycles recorded before stellate stimulation.

With each successive cycle, the P-wave became progressively elevated in association with the pacemaker shift to the right atrium and concomitant
Five of eight consecutive cycles showing pacemaker shifting from the region of the SA node to a site in or near the anterior internodal pathway. Continuous left stellate stimulation beginning six seconds prior to cycle depicted in panel A.
re-alignment of supraventricular conduction. In panel C electrical activity appeared almost simultaneously in the internodal pathways and the right atrial recording sites while panel E shows a 5 msec interval between right atrial and internodal pathway depolarization with RA precedence.

The time interval between posterior internodal and left atrial excitation shortened with each successive cycle but increased with respect to the right atrial electrode deflection. Thus, LA excitation remained approximately 20-25 msec behind the initial electrical activity regardless of the precise location of the pacemaker. Panel A also shows that RA and LA were excited almost simultaneously, whereas a more nearly normal interval of approximately 15 msec exists when the pacemaker is in or near the SA node (panel E).

An illustration of the influence of left stellate stimulation upon a sinus rhythm is shown in figure 4. Panel A reveals a typical sinus pattern of depolarization and is identical to traces recorded during the control period. The five panels presented were taken from eight consecutive cycles occurring six seconds after the onset of stimulation. P-wave configuration and P-R interval in the ECG traces were normal. Moving toward panel E there was progressive shortening of the P-R interval with a concomitant synchronization of internodal activation patterns. P-wave amplitude remained essentially unaltered until a change of configuration in the electrograms (MIN) (PIN) occurred in panel D. With a minimal diminution of P-R interval there appeared a significant reduction in P-wave amplitude as compared with panel C. One cycle later (panel E) the activation sequence
TABLE I

<table>
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<tr>
<th>Pattern Designation</th>
<th>SRa</th>
<th>SRb</th>
<th>SRc</th>
</tr>
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<tbody>
<tr>
<td>SA</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>AIN</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>MIN</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>PIN</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>LA</td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Frequency of occurrence in %

|          | 56% (15) | 33% (9) | 11% (3) |

Three variations (SRa, SRb, SRc) in atrial conduction observed with SA nodal rhythm (SR) as a result of right stellate stimulation in 14 experiments. The order of onset of activity in the individual electrograms is represented by the numerical sequence. Relative percent incidence and number of cases (in parentheses), for each pattern are also given.
was dramatically altered to that of a Bachman's bundle (AIN) rhythm. This was reflected in the ECG by a P-wave of minimal positive amplitude and a scarcely discernible P-R interval.

The alteration in P-wave configuration can be explained by a change in vectoral representations of atrial depolarization associated with a Bachman's bundle rhythm. Because of the bi-directional transmission of the depolarization wave from this pacemaker site, a reduction in the summated vector results in a decrease in detectable potential.

It is recognized, of course, that precise localization of the pacemaker is not possible in preparations utilizing only a limited number of unipolar leads. However, the profound changes in activation sequences at the six selected electrode positions, as shown in figures 2, 3, and 4, strongly suggest variations in pacemaker site.

Changes in activation sequences as a result of right stellate stimulation are summarized in table I. A total of 27 measurements were made on the 14 preparations during this procedure. In all but one instance the patterns occurring with right stellate stimulation were different from those associated with the control state. Those rhythms characterized by initial SA node activity were then categorized according to their internodal sequence pattern. The resulting three patterns were listed in terms of their relative percent occurrence. Two measurements were made in each animal in all but one instance.

Three distinct patterns, with initial SA nodal depolarization, are designated SR-\(a\), SR-\(b\), and SR-\(c\). The SR-\(a\) (sinus rhythm-\(a\)) pattern con-
Electrogram and ECG recordings of control, right and left stellate stimulation with the SA node intact. Control sinus rhythm shown.
sisted of AIN depolarization immediately following the sinus region potential. Activity subsequently and successively reached MIN, LA and PIN. This pattern of atrial electrical excitation was most common with an incidence of 56% of the total. Intermediate in occurrence was the SR-b pattern represented in 33% of the right stellate stimulations. Reversal of the temporal relationship between PIN and LA and that of AIN and MIN, differentiates this pattern from SR-a. Least in evidence, with a 11% incidence, was the SR-a pattern while the PIN-LA relationship followed that of SR-b.

To negate the likelihood of measurement error, all measurements were made during the maximal heart rate response elicited by the stimulation. Random measurements made at different times during the period of sustained, maximum heart rate suggested constancy of a given pattern during stimulation.

B. SUPRAVENTRICULAR PACEMAKER SHIFTS BEFORE AND AFTER SA NODE EXCISION. Twelve mongrel dogs were prepared as previously described. Data for periods of control, right and left stellate stimulation were recorded prior to (pre-excision) and after (post-excision) the SA node was surgically excised.

Figure 5 shows the expanded record from an experiment in which a control sinus rhythm was demonstrated. Initial depolarization was noted to occur at the RA electrode, followed by the sequential activation of AIN - PIN - MIN - LA. The ECG configuration was an expected sinus pattern with a heart rate of 135/min. Right stellate stimulation (RSS) increased sinus rhythm rate (185/min) and synchrony of atrial activation, resulting in a decreased P-R interval and heighten P-wave amplitude.
Electrogram and ECG recordings of control, right and left stellate stimulation after SA node removed. Control posterior internodal rhythm shown.
Transmission of the depolarization wave was modified by RSS, exemplified by the change in the internodal excitation pattern (AIN - MIN - PIN - LA). Enhancement of atrial electrical synchrony was demonstrated by the shortening of RA to LA activity.

Left stellate stimulation (LSS) resulted in alterations in both individual electrograms and the site of initial detected depolarization. These changes were accompanied by a marked reduction in P-R interval and P-wave amplitude, though heart rate (140/min), was not significantly different from control. Electrogram traces show that all internodal depolarizations precede activity in the RA and LA, indicating a more centralized pacemaker position between the atria. This is supported by the initial activity observed at the AIN lead, in the superior margin of the interatrial septum.

This pre-excision state is compared with results obtained after SA node excision in the same preparation (Figure 6). The control panel illustrates dramatic changes in atrial depolarization as a result of the extirpation procedure. A low, amplitude, biphasic P-wave was recorded with a heart rate of 90/min., a 30% decrease from the pre-excision control.

Electrogram examination reveals a control coronary sinus (PIN) rhythm. RSS shifts the initial activation to the AIN region as shown in the center panel. Interestingly, the resulting activation sequence and ECG trace was not unlike that observed with pre-excision LSS. This phenomenon of post-excision RSS causing pacemaker activity and activation sequences identical, or very similar to pre-excision LSS, was noticed repeatedly.
### TABLE II

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>RSS</th>
<th>LSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-excision</td>
<td>137.9 ± 5.4</td>
<td>210.8 ± 8.2</td>
<td>163.3 ± 4.9</td>
</tr>
<tr>
<td>Post-excision</td>
<td>120.4 ± 4.3</td>
<td>167.9 ± 5.7</td>
<td>160.0 ± 5.3</td>
</tr>
<tr>
<td>Significance</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.005</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

Comparison of heart rates for control, right and left stellate stimulation for 12 experiments. Values are given for periods before and after SA node excision. Means, standard errors and the statistical significance between values observed with intact and excised SA node. Average heart rates for control periods preceding right stellate stimulation (137.9 ± 5.45) and preceding left stellate stimulation (137.9 ± 5.59) were not statistically different.
Electrogram and ECG recordings of control, right and left stellate stimulation with SA node intact. Control middle internodal rhythm shown.
The heart proved responsive to the action of sympathetic stimulation (HR=145/min), though maximum response was diminished to a level comparable with that induced by LSS.

Stimulation of the left stellate increased heart rate to 140/min., instituted AIN electrical precedence and resulted in an ECG trace having a low P-wave and short P-R interval. All changes also having been produced with LSS prior to SA node removal.

Comparisons of mean heart rates before and after removal of the SA node are shown in Table II. Figures for control, right and left stellate stimulation are shown. Control rates, after SA node excision, were found to be significantly decreased from the pre-excision state (p < 0.05) as were those following right stellate stimulation (p < 0.005). However, alterations in LSS rates were not found statistically different.

Though the SA node was removed, and spontaneous heart rate diminished, regular rhythm persisted and the chronotropic mechanisms remained responsive to extrinsic nerve stimulation. It is also interesting to note the similarity between the mean rate for post-excision RSS and either LSS mean.

Figure 7 demonstrates the existence of spontaneous internodal rhythms. Initial activation occurred in the MIN electrode from whence it spread to PIN-AIN-RA-LA. Of considerable importance was the appearance of a 'normal sinus' ECG trace. Changes surely would have been detected had vectorcardiograms or multiple limb leads been used, but lead II failed to differentiate the nodal from the non-nodal rhythm. The presence of an inverted electrogram trace in RA as compared with the pre-excision state
Electrogram and ECG recordings of control, right and left stellate stimulation with SA node removed. Control middle internodal rhythm shown.
was noted. This was thought to reflect a change in the ground circuit due to the presence of the atraumatic clamp left on the atrium after SA node excision.

With RSS, SA node excitability increased so as to institute the 'normal' sinus pattern of activation. Heart rate climbed to 220 in association with expected ECG recordings.

LSS produced a coronary sinus (PIN) rhythm, most often seen with this type of stimulation. The P-wave is close to the QRS, and of low amplitude, while the heart rate was elevated to 170/min. It was noted that coronary sinus rhythm could be associated with either low amplitude, biphasic or inverted P-waves. However, these configurations were found to vary predictably according to the activation sequence of the other recorded areas. Thus it appears that differences in directional conduction and pacemaker site may be involved in the genesis of a family of rhythms collectively termed from coronary sinus origin.

In the animal just described, the SA node was then excised. (Figure 8) Though less synchronous, the activation sequence resembled the control trace prior to surgery. MIN precedence was maintained and HR fell slightly to 130/min. Even with these apparent similarities, evidence for modification of atrial conduction because of SA excision was found in the ECG. The P-wave is low and multiphasic. Such a trace probably reflects the activation of distant aspects of the atria now relatively, electrically separate. This being the outcome of unavoidably disjoining the internodal tracts at their superior end concurrent with SA extirpation.
Distribution of initial depolarizations detected at the given electrode sites during control, right and left stellate stimulation before (pre-excision) and after (post-excision) SA node excision. Results of 12 experiments are shown.
Unlike figure 7 in which the SA was present, after its removal, RSS did not restore sinus rhythm. A coronary sinus rhythm was initiated having a rate of 190/min. After an adequate recovery period the control MIN sequence was resumed, after which LSS induced PIN dominance. Again, the presence or absence of the SA node did not alter the response to LSS as heart rates, activation sequences, and ECG traces were comparable.

Pacemaker distribution (Figure 9) is shown for control, right and left stellate stimulation for both pre (upper graphs) and post-excision (lower graphs) periods. This chart represents a summary of over two hundred rhythm measurements, in twelve animals or approximately 40 each for the intact SA node periods and 25 each after SA removal. All bars depict the relative percent incidence which its labelled area was observed to demonstrate initial depolarization activity during a given period.

With an intact SA node, spontaneous sinus rhythm (SA) occurred with a 69% incidence. No AIN rhythms were demonstrated. MIN accounted for 20% and PIN 11% of the control pacemaker activity. RSS shifted the pacemaker sites toward the SA node region (93%) at the expense of internodal precedence. LSS proved to display the widest variability of sites. The trend is to non-nodal areas with sinus rhythms having minority representation (31%). 50% of the stimulations resulted in a coronary sinus sequence. A-V nodal rhythm was observed in only 15% of the recordings.

After SA node excision and reimplantation of the RA electrode at various points next to the incision, this region (SA) failed to initiate depolarization. MIN precedence represented 72% incidence, implicating MIN as a highly excitable area. With right stellate stimulation the tendency
Transverse histologic section of specimen removed from the SA nodal region showing atrial muscle at both borders of the nodal tissue. Previous placement of the RA recording electrode is illustrated by the tissue separation within the node.
toward excitation in upper atrial areas remained, as institution of AIN pacemakers clearly indicates.

Not surprising were the relatively minor shifts between pre and post-excision traces with LSS. This was suggested by the apparent lack of alterations between ECG traces and attained heart rates seen in the individual experiments.

The consistent initiation and elevation of MIN rhythm after SA node excision in both control and stimulation periods, point to intrinsically excitable and neurogenically responsive foci in this region.

A transverse section of atrial myocardium is shown and represents that tissue which was removed surgically at the SA node region (Figure 10). All SA nodal tissue was considered excised when histologic evidence of true atrial muscle was seen to completely encircle the node. This was found in all specimens sent for histologic verification and includes nine of the twelve excision experiments.

The thinner atrial muscle wall is seen at both edges of the SA node tissue. Atrial supply to the node is demonstrated by the SA nodal artery seen at the periphery of the node. Separation of the tissue within the node is also seen and represents the site of the RA electrode prior to SA node removal.
CHAPTER V
DISCUSSION

This study, designed to examine pacemaker activity induced by sym­pathetic stimulation, serves to point out discrepancies inherent in the convention which consigns 'normal' pacemaker function to one localized point within the supraventricular myocardium. Continuous monitoring of atrial area depolarizations using multiple recordings were utilized to detect changes in depolarization activity. Measurements of the alterations in initial site of activation during control and stimulation periods were thought to reflect changes in atrial pacemaker location and relative con­duction velocities. Separation of the relative roles of these two phenomena were not possible owing to the inability of the present equipment to measure conduction velocities. However, the time magnitudes involved in the separation of SA nodal from non-nodal rhythms were such as to severely limit the attribution of the various detected sequences to changes in con­duction velocities alone.

Related questions of these direct electrical recordings have been clearly stated and evaluated by Mirowski et al (1970). These authors
stated that 1) the electrode recording the earliest electrical activity is located close to the impulse forming center, 2) the possibility that sustained ectopic atrial activity might be caused by the electrodes themselves was recognized but thought to be improbable. These conclusions were independently arrived at during the course of the present experiments and were incorporated in the determination of the results. Also, recordings at the area of the bundle of HIS were found to be inconsistent and were not used in any measurements critical to the validity of this study.

Spontaneous shifts in the origin of atrial excitation have been shown using both direct and limb lead recordings (Brody and Woolsey, 1967) (Woolsey and Brody, 1967) (Spach, et al, 1969). Such changes observed with electrocardiographic techniques in the intact preparation have been correlated with exercise and augmented sympathetic discharge (Irisawa and Seyama, 1966).

The possibility that pacemaker centers may exist in the left atrium was recently emphasized by their demonstration in more than 70% of dogs tested (Mirowski, et al, 1970). Such left atrial beats were observed to occur spontaneously, during vagal stimulation, after destruction of the sinus node, and during ventricular pacing. Left atrial pacing through the electrode recording initial activity reproduced the same sequence and configuration of atrial electrograms observed in the spontaneous left atrial beats.

Hoffman and associates have carefully differentiated the transmembrane potentials of single fibers in the SA node, in true atrial muscle, and atrial tissue having properties similar to those of the ventricular Purkinje system. They recognized the presence of latent pacemakers in the
latter tissues of the right atrium but state "we have never recorded the development of pacemaker activity in ordinary atrial muscle fibers" (in dogs, cats, rabbits and rats), (Hoffman and Cranefield, 1960). Hoffman's experiments show that non-SA nodal foci were always located in specialized fibers. Accepting the premise that pacemaker potential is primarily, if not exclusively confined to these specialized tissues, it is reasonable to conclude that non-nodal supraventricular pacemakers are located within the purkinje-like fibers of the internodal conduction pathways.

Alterations in atrial conduction and pacemaker activity were noted to occur both spontaneously and during sympathetic stimulation. A change in the excitability of atrial internodal tissue was thought to account for those alterations and that the level of excitability depended upon two basic mechanisms: 1) the influence of extrinsic nerve activity, 2) the basal intrinsic excitability of the tissue itself. The combined effects of these two mechanisms would determine tissue excitability at any given moment, the former being subject to artificial manipulation.

With both cervical vagosympathetic trunks decentralized, the inhibitory parasympathetic component could be eliminated. Then, with stimulation of the sympathetics, the effects of alterations in the extrinsically mediated conductile tissue excitability could be studied.

It was shown that right and left stellate stimulation revealed markedly different results. This was thought to be a reflection of the variation in local sympathetic nerve distributions. Increased firing rate of the SA node was readily accomplished through excitation of right sided fibers which
released catecholamine at receptor sites capable of increasing membrane depolarization (Hutter and Trautwein, 1956). Norepinephrine concentrations are known to be significantly higher in the SA node region than in other atrial tissue (Shindler, 1968). However, left stellate excitation generally elevated the excitability state of lower portions of the atrium to levels permitting assumption of pacemaker activity. Presuming the mechanism of this resides in a comparable release of norepinephrine at a non-nodal site the present hypothesis suggests selective innervation of the internodal conduction pathways by the left sympathetics. The frequent localization of pacemaker site in or near the coronary sinus, was interpreted, in this view, to represent either an area of particularly high concentration of left sympathetic nerve terminations or a site of high intrinsic sensitivity to norepinephrine stimulation. Insignificant changes in heart rate and small differences in pacemaker activity with LSS before and after SA node excision support this view of left sided innervation.

The overwhelming incidence of 93% sinus rhythm with RSS pointed to the distribution of right sided innervation to this highly excitable tissue. This was reflected by the mean attained heart rates of the SA nodal rhythms. However, the precedence of pacemaker activity in the AIN and MIN regions with RSS after SA excision, supported the contention that right sympathetic distribution to these areas was masked by the presence of an intact SA node. The primarily upper atrial distribution of the right sided sympathetics was also suggested by the tendency toward AIN pacemakers upon stimulation.

Spontaneous alterations of pacemaker location with an intact SA node
supported the concept that differences in SA node and internodal excitability (mainly MIN) were not always distinct in the decentralized preparation. The 72% incidence of spontaneous MIN rhythms after SA node excision confirms the excitable nature of this area.

Of considerable interest was the similarity of mean heart rates observed for post-excision RSS and LSS. Though the primary locations of pacemaker sites varied, the possibility exists that these rates reflect the excitability potential common to internodal tissue under supramaximal sympathetic stimulation conditions.

Speculation as to the relative role of the parasympathetics on pacemaker activity was considered. By implicating local release of acetylcholine through nerve stimulation, local pacemaker activity could be inhibited. Where the distributions of sympathetic and vagal fibers overlapped, pacemaker induction by sympathetic stimulation should be antagonist by the concurrent activation of the parasympathetic component. Such an hypothesis has been confirmed by this author in other experiments. These findings serve to emphasize the significant inter-relationship inherent in local distributions of autonomic fibers to discrete areas of the myocardium.

The changes observed in atrial depolarizations as manifested by shifts in activation sequences were also dependent on the excitability state of the conductile tissue. Changes were thought to be due to the combined effect of alterations in conduction velocities, exit phenomenon, and grossly undetectable shifts in pacemaker location. These modifications in conductile tissues, though less striking than actual gross pacemaker shifts, probably
lie along their spectrum of excitability just short of pacemaker manifestation.

Though pattern alterations were observed with both RSS and LSS, changes were more purely evident with RSS, owing to the fact that they occurred more often in the absence of an actual pacemaker shift. The dominating influence of the sympathetically stimulated sinus node with RSS did not allow for shifts in pacemaker to another site and therefore allowed independent examination of atrial activation.

To validate both pacemaker shifts and atrial depolarization changes observed with these recording techniques, pacing of the heart was done at the specified sites from the internodal recording electrodes. Patterns of atrial activation were found to fall within the spectrum seen during spontaneous discharge from these same areas. Coronary sinus pacing was especially duplicative of the spontaneous state as diminished atrio-ventricular activation time was also seen in both.

In order to achieve reliable direct recordings of depolarization activity, it was necessary to perform the following maneuvers: intravenous administration of an anesthetic agent, open chest surgery, inflow occlusion technique, and decentralization of vagal and sympathetic nerves. Though it is realized that changes from the physiologic state could be the result of these manipulations every effort was made to minimize these proposed changes.

During inflow occlusion, time at zero cardiac output was strictly limited to within one minute. No animal was included in this study unless the spontaneous rhythm after surgery, as judged by ECG and four epicardial
recordings was identical to that seen prior to the occlusion technique. Inadvertent damage to autonomic nerves coursing down the SVC was circumvented by careful dissection prior to insertion of the loop snares.

The incision of the RA was limited to the minimum size which the intra-atrial structures could be visualized. Moreover, incision placement was such as not to interrupt any known conduction pathways or major blood supply to these conductile structures. To substantiate the argument that neither the incision nor the inflow procedure itself was altering atrial conduction, pilot studies were conducted in which only epicardial electrodes were incorporated. By this means activity at all internodal pathways could be recorded except for MIN. Records of the incised group were compared to the non-incised studies and were found to show no differences in the acquired data. These safeguards, along with the results of supraventricular pacing, lead this investigator to believe that the minimum possible disturbances in physiologic activity were incurred through these experimental procedures.

Confirmation of the changes in the ECG as seen by Brody and Woolsey in the spontaneously beating heart were also observed in these studies. It was found that these changes were a reflection of the individual electrogram traces which confirmed actual pacemaker shifting. Stimulation of the right stellate decreased the variability of P-wave morphology which reflects the almost perfect positive correlation between RSS and sinus rhythm. LSS was found to cause the highest degree of differences in P-wave and P-R interval. This too, was expected as LSS resulted in the most variable distribution of pacemaker sites.

There is difference of opinion concerning polarity and configuration
of the P-wave in coronary sinus rhythms. Moore et al (1967) and Mussumi et al (1967) found inversion to be inconsistent or absent in leads II, III and a VF, while Lancaster et al (1965) and Damato and Lau (1969) consistently found P-wave inversion in these leads. Figure 3A of these experiments shows an almost isopotential coronary sinus rhythm P-wave, a position somewhere between those of the above investigators. However, variability of the P-wave with initial activity in the PIN lead did occur and these changes were associated with changes in activation patterns. Therefore, although this author is in agreement with the findings of Damato and Lau as to the coronary sinus location of the pacemaker, variations in atrial propagation associated with this pacemaker site do not substantiate their concept of a consistent P-wave configuration associated with this pacemaker site.
Supraventricular pacemaker activity and atrial activation were studied using multiple electrode recordings in conjunction with a time-scale expansion technique. Area depolarizations were recorded at specific sites along the atrial conduction pathways during control, right and left stellate stimulation. Analysis of the data revealed the following:

1) Shifting supraventricular pacemakers were found to occur spontaneously in non-SA node sites during 31% of the control period.

2) RSS increases sinus supremacy of pacemaker activity to 93%

3) LSS causes the most variability in pacemaker location with only 31% at the SA node.

4) Removal of the SA node surgically, results in drastic changes in pacemaker activity during both control and RSS but has little effect on LSS induced pacemakers.
5) Sympathetic stimulation frequently alters sequence of atrial activation.

6) Lead II ECG did not necessarily distinguish between sinus and non-nodal rhythms.
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APPROVAL SHEET

The thesis submitted by John M. Geesbrecht has been read and approved by four members of the faculty of the Graduate School.

The final copies have been examined by the director of the thesis and the signature which appears below verifies the fact that any necessary changes have been incorporated, and that the thesis is now given final approval with reference to content, form and mechanical accuracy.

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

May 31, 1976

Date

Signature of Advisor