Multicentric Origin of the Atrial Depolarization Wave: The Pacemaker Complex

Relation to Dynamics of Atrial Conduction, P-Wave Changes and Heart Rate Control


SUMMARY In studies to ascertain the basis of dynamic changes in the P wave, bipolar epicardial potentials were recorded from multiple atrial electrodes in dogs. One hundred to 120 activation times were displayed by a digital computer and used to construct atrial isotemporal activation sequence maps. Changes in heart rate or beat-to-beat cycle length were induced by vagal stimulation or infusion of autonomic mediating drugs. Changes in cycle length were associated with dynamic changes in the atrial activation sequence and surface P-wave. A conspicuous finding was that epicardial atrial depolarization began at three widely separated locations. These three points were consistently present in all animals and were generally located at the 12, 3, and 6 o’clock positions of the superior vena cava-right atrial junction. The dynamic changes in P waves and atrial activation sequence which accompanied the changes in cycle length were due to sudden shifts in the point of earliest activity between the three early sites. Asymmetric atrial depolarization with more rapid conduction along the crista terminalis, superior interatrial band, and pectinate muscles was present in all dogs. Although the anisotropic atrial geometry played an important role in the asymmetric conduction, the widely distributed onset of activity contributed significantly to the uneven spread. The multiple points of origin of the atrial wavefront might be explained by either a trifocal, distributed pacemaker or the epicardial exits of three specialized pathways conducting an impulse emanating from a single focus. These data explain the dynamic variation in P-wave morphology in normal hearts and also imply a relationship between the altered origin of atrial depolarization, atypical P waves, brady- or tachyarrhythmias, and heart rate control.

This study was designed to determine the basis for changes in the configuration of the P wave in the surface ECG. We were aware of beat-to-beat changes in P waves accompanying heart rate variations in normal human subjects. We were also aware of changes in which transient forms of the P wave exhibited extreme notching and prolonged duration, resembling left atrial enlargement or atrial conduction delay. Because these patterns were unstable, changing back to normal, we suspected they might represent dynamic variations in the atrial activation sequence, resulting in delayed left atrial activation.

As a working hypothesis we considered that each different P-wave morphology reflected a particular atrial activation sequence and that a change in the P-wave configuration was the result of a dynamic change in the activation pattern. We also hypothesized that a change in the P wave would be associated with a change in the atrial pacemaker location, with each new pacemaker site determining a new atrial activation pattern which would be reflected at the body surface as a new P wave. To evoke changes in atrial activation and the surface P wave in dogs, we used vagal stimulation, vagolytic, adrenergic and adrenolytic drugs, to alter the cardiac rate and autonomic balance. We hoped to see if changes in rate were accompanied by predictable changes in the atrial pacemaker location and activation sequence.

The prevailing concept of atrial depolarization is that the normal impulse is initiated within the sinus node and appears shortly thereafter at a single focus on the atrial epicardium very close to the pacemaker, from where it spreads to the rest of the atria. Furthermore, it is believed that when the pacemaker shifts to a different site that this area becomes the new focus from which the activation wave emanates and depolarizes both atria, including the former point of origin. In the present study in dogs we found that depolarization was initiated from multiple right atrial sites. Three separate points of origin were consistently noted, and two of these were found at positions outside the sinus node region. This new evidence indicates that the mechanism of initiation of the excitation wave differs from the classical description of a single, dominant focus and is more accurately represented by a pacemaker complex.
Methods

Thirty mongrel dogs weighing 20-30 kg were studied. Twenty-four were anesthetized with an initial I.V. dose of 30 mg/kg of sodium pentobarbital. A midsternal thoracotomy was performed and the heart cradled in the pericardium.

Individual bipolar electrodes were attached to the left atrium and around pulmonary veins with small stainless steel hooks. Two templates with a total of 96 bipolar electrodes were sutured to the atrium, as illustrated in figure 1. The sutures were placed so as to avoid disruption of the activation sequence. The electrodes were 0.2 mm silver balls with a separation of 1 mm between bipolar points. There was a distance of 3 mm between each bipolar recording pair of electrodes (spatial resolution of 4 mm). In each study we used between 108-120 bipolar electrode pairs. The electrodes were connected to a 28-channel data acquisition system. The bipolar data were recorded at a frequency response of 100-2000 Hz. Three external ECGs (leads 1, 2 and 3) were recorded at a frequency response of 1-200 Hz. All data were recorded on a 28-channel FM tape recorder. Simultaneously, the data were digitized and timed relative to an atrial reference electrode using a PDP-11 with a resolution of 1 msec. The sampling rate for the timing program was 1000 samples per second. A threshold rate of change of voltage \( \frac{dv}{dt} \) and voltage product were selected and entered into the program. The time of local activation was selected by determining the greatest product of \( \frac{dv}{dt} \) and voltage greater than the threshold and within a 7-msec window.

Maps of each transient state of atrial activation and P-wave configuration were produced from 108-120 bipolar electrodes recorded 24 at a time. The successively recorded sets of 24 electrograms were temporally related to the same reference electrogram.

**Figure 1.** Mapping methods. Atrial epicardial bipolar potentials were recorded from fixed templates of multiple electrodes and individual sites (top left panel). Groups of 24 potentials were recorded simultaneously with a reference electrogram and surface leads 1, 2 and 3 (right panel). Activation times for 108-120 atrial locations were obtained and displayed by digital computer (lower left panel).
which was recorded from the RA appendage with each set. The earliest electrogram was used as zero or onset time.

Early in the study we established that changes in P-wave morphology were associated with changes in atrial activation sequence. We determined this by recording a subset of 24 electrograms, widely distributed over the RA template, with the surface P waves and a reference electrogram. P waves of identical morphology by visual inspection and superposition, together with reference electrograms which occurred at the same instant in relation to the P wave, were always associated with less than 2-msec differences in the activation times at all 24 points. In processing the final 108–120 point maps, and to insure that the activation was the same for each 24-point recording, several checks were made. First, only data with the same P-wave morphology was accepted. Second, each map was constructed at several times under the same experimental conditions. As a third check, the subset of 24 points distributed all over the large RA template was used to construct a map. This map was compared with a map constructed from the three 24-point sets taken from three beats. The maps were very consistent when checked by all three methods. Finally, three successive 108–120 point maps were made for each state (each different rate, P wave, etc.) and compared for variance. The reproducibility of the dynamic state and final maps were judged to be acceptable if the activation time variance in all of the 108-plus points was no greater than 2 msec in comparing the three maps produced for each state.

Interventions used to alter the heart rate or change the atrial activation sequence were carefully controlled to repeatedly reproduce the same rates, P-wave morphologies and reference timing. Three techniques were used to change the dog’s heart rate. The rate was decreased by the use of vagal stimulation and by the administration of propranolol. The rate was increased by the use of isoproterenol. For vagal stimulation the right cervical vagosympathetic trunk was exposed and a bipolar electrode attached. Stimulation was done at a rate of 15 pulses per second with the stimulus strength (mA) set to obtain the desired heart rate. Termination of vagal stimulation resulted in an almost immediate return to control normal sinus rhythm conditions. Propranolol was administered intravenously in a dose of 1–4 mg. The dose was adjusted to obtain the desired heart rate. Because of the long-lasting effects of the drug, it was usually infused as the last procedure in the experiment. The heart rate was increased by the use of isoproterenol administered intravenously at a rate of 4 μg/min through a drip set. The drug was administered for the period of time necessary to produce the desired heart rate and to record the data. Five minutes after the cessation of administration of the drug the dog returned to normal sinus rhythm. However, to insure that the effect of the drug had worn off completely, one-half hour was allowed between recordings.

Usually the activation maps were made in the following order: a normal sinus rhythm control map was made, then vagal stimulation maps were made at a rate reduction of approximately 15% and then 30%. After vagal stimulation, a normal sinus rhythm map was made to insure that no long-term changes were caused by vagal stimulation. Third, the rate was increased by approximately 15% and 30% with an isoproterenol drip. After approximately 30 minutes another normal sinus rhythm map was made. Finally, the propranolol map was made with a rate reduction of 15–30%

Early in the study we found that each different ECG P wave was due to a different global atrial activation pattern. We also observed that the activation sequence and P wave changed at different heart rates. In addition, we noted that the earliest points of activation moved. To test whether the change in global atrial activation was a result of the change in onset sequence or was due to some direct effect on the atrial myocardium and local conduction resulting from the techniques used to modify heart rate, i.e., drugs, vagal stimulation, etc., the following experiment was performed. In six dogs the atria were driven at a constant rate 30% above the spontaneous sinus rate. The right atrium of each dog was paced from three to four locations and maps of the activation sequence were made. Subsequently, the same locations were driven at the same rate, but in addition, the vagus was stimulated and later atropine, isoproterenol and propranolol were infused as described previously. Comparisons of activation maps from identical pacing sites with and without the added intervention revealed no differences. These findings indicated that site of origin, and not altered local conduction, accounted for the changes in activation and P-wave patterns.

Because of the high basic heart rate in the 24 dogs which were anesthetized with pentobarbital, six dogs were premedicated with 1 mg/kg morphine sulfate I.V. and anesthetized with 80 mg/kg α chloralose I.V. This anesthetic agent was used to insure that the observed activation sequences, dynamic variations, etc., existed over a wide range of heart rates and were not artifacts created by the pentobarbital. The slow rates produced with this anesthesia were associated with marked beat-to-beat changes in cycle length and P-wave form. Thus, our observations were made over an extended range of heart rate, autonomic balance and pacemaker function.

The interventions employed to change atrial activation and P wave were controlled to avoid atrioventricular (AV) nodal, low atrial or other rhythms where the initial activation occurred distant to our sampling electrodes. We therefore limited our observations to changes of the outer atria, sometimes referred to as intranodal shifts.

At the end of each study the animal was sacrificed and the heart, trachea and lungs were removed together. The hearts were washed in 0.9% saline and fixed in 10% buffered formalin solution. Later the atria were dissected and photographed using a special transillumination technique to demonstrate major
atrial muscle bands and areas of myocardial concentration. Subsequently, the individual activation times were related to the transilluminated structures by noting the previous points of attachment of the templates and the individual electrodes (fig. 2).

Results

Our primary objective was to understand the dynamic mechanisms of change in the P wave rather than to explain in detail the genesis of the total waveform. Thus, we concentrated on obvious changes in the patterns of peaks, notches and changes in duration in leads 1, 2 and 3.

Atrial Anatomy, Activation Times, and Activation Sequence Map

Figure 2 relates atrial activation to the transilluminated anatomy of the atria viewed posteriorly. The activation times indicated in figure 2A correspond to the locations of electrodes in figure 1. Activation times are shown for only 37 of the 112 points explored in this dog. Note that the earliest activation times are located over darker bands of dense myocardium corresponding to the superior (anterior) interatrial band and crista terminalis. The isotemporal map in figure 2B was constructed from the 112 activation times. Each isotemporal line represents the approximate position of the wavefront at each designated instant.

Multicentric Onset of Atrial Activation

Three discrete areas of activation onset or origin points (referred to as O-points) were demonstrated in 29 of 30 dogs. These points were generally located at the high, mid, and low (12, 3 and 6 o'clock) positions of the superior vena cava (SVC)-RA junction (fig. 3). The O-points are designated by A, B and C for the upper, middle and lower positions, respectively. Although O-point B was located over the crista terminalis and near the position of the sinus node, O-points A and C were located 10–20 mm away from sinoatrial (SA) node area. O-point C was occasionally located at a somewhat lower position, to the right of the upper limit of the inferior vena cava along the lower crista terminalis. Also, O-point C, although the most inferior of the three, was located 1.5–2 cm above the low right atrium and coronary sinus, and far from the frequently described, subsidiary atrial pacemaker.
regions. The three O-points were typically separated by a distance of 12–20 mm, and each point was surrounded by significantly later activation times. The onset of activation was not necessarily simultaneous at all three O-points. Frequently, early activation at one O-point was followed by the later appearance of activation at the other two areas. Although delayed, these O-points were still surrounded by even later activation times, indicating that these locations continued to be points of depolarization origin. It is likely that even the dog with only two obvious origin points actually had three. A third area was present which consistently demonstrated activation times 1 msec earlier than surrounding regions. However, because of the 2 msec timing error limitation, we could only be certain of two points of origin.

The onset sequence of O-points A, B, and C is represented as A-1, B-2, C-3, or B-1, A-2, C-3, i.e., the point with earliest activation time listed first, etc. There was no absolutely consistent sequence of O-point activation. More dogs exhibited a B-1, A-2, C-3 sequence than any other pattern; however, simultaneous activation of points A and B, followed by C, was also common. Frequently, at the higher basic rates, in dogs anesthetized with pentobarbital, O-point C was not apparent, manifesting considerable delay relative to A and B and being depolarized from these superior O-points. In these animals the con-

Figure 3. Multicentric origin of atrial depolarization wave. The isotemporal map in A demonstrates the origin of atrial depolarization from three points which excite simultaneously at the 12, 3 and 6 o’clock positions in relationship to the superior vena caval-right atrial (SVC-RA) junction in dog 14. Note that the activation wavefront at 10 and 20 msec is elongated predominantly in the superior-inferior axis corresponding to the position of the crista terminalis. Additionally, note that the wavefront between 0 and 20 msec depolarizes most of the right atrial body corresponding to the low amplitude initial deflection of the P wave shown below. Activation of the left atrium occurs from 30–70 msec and corresponds with the second component of the surface P wave. The three early sites are identified by A, B, and C shown in panel B. In panel B, note that when the wavefront originates from all three sites there is rapid depolarization of the inferior right atrium; however, when only the two upper sites initiate atrial depolarization (panel C) the wavefront has traveled only as far as the lower SVC.
The asymmetry of atrial depolarization was readily revealed by interventions used to slow heart rate, i.e., vagal stimulation and propranolol infusion. The sequence of atrial activation during stable sinus rhythm in relation to the lead 2 P wave is shown in figure 3A. During stable atrial rhythms and rates above 120, the atrial activation patterns were typically asymmetrical. The asymmetry was characterized by irregular projections of the wavefront leftward, rightward and inferiorly from O-points A, B and C, respectively. The asymmetry was due to the interaction of two factors: first, the widely distributed, multicentric origin of the depolarization wave, and second, a preference for conduction in specific directions away from the three O-points. This latter effect was related to the unique arrangement and concentration of atrial myocardium in thick bands (fig. 2A). Superimposition of activation times onto the transilluminated anatomy demonstrated that the axes of maximum conduction velocity were aligned with the axes of the superior interatrial band, crista terminalis and major pectinate muscles. The influence of each O-point on the pattern of asymmetric activation became more apparent with a change in O-point sequence. Delay or disappearance of early activity at one of the O-points resulted in obvious changes in the asymmetric pattern (figs. 3B and 3C). In the example shown in figure 3B and 3C, the loss of early activity at O-point C resulted in delayed excitation of the inferior right atrium (compare the relative positions of 20-msec wavefront with and without participation of O-point C).

To rule out a common SVC focus propagating fingerlike projections of activity to the separate O-points, extensive SVC-RA junction mapping was performed in six dogs. In these animals, activation was recorded from 96 points on the right atrium and 48 points at the SVC-RA junction, and the isochronous maps were constructed from the 144 points explored. The data was consistent in all six dogs; a map of one dog is shown in figure 4. During control sinus rhythm, the earliest site of activation was on the immediate

**Figure 4.** Map of activation at the superior vena caval-right atrial (SVC-RA) junction. Panel A shows the atrial activation sequence from a right, posterior view, and B shows it from an anterior view in dog 27. Arrows indicate peripheral regions where no potentials were recorded. Panel C shows the P wave and time key for the activation during spontaneous sinus rhythm demonstrated in panels A and C. Note the bifocal origin of depolarization at the upper (4 msec) and middle (0 msec) O-points. A third origin point inferiorly was revealed by vagal stimulation. T = tricuspid area; M = mitral area; IVC = inferior vena cava.
RA side of SVC-RA junction in three dogs and on the immediate SVC side in the other three. In the dog shown in figure 4, activation appeared first at the middle O-point before the onset of the P wave in the ECG. Four milliseconds later a second focus of activation appeared at the upper O-point. We were not able to demonstrate a common caval origin of activation linking separate O-points in any of the dogs. In figure 4 the lower O-point was concealed during the control sinus rhythm shown here but was evident with vagal stimulation.

Changes in rate or beat-to-beat cycle length were accompanied by changes in atrial activation and the surface P wave. The relation between cycle length, activation, and the P wave was characterized by two degrees or magnitudes of change: 1) a subtle continuum of slight change in activation within a range of increasing or decreasing cycle lengths; and 2) a marked, abrupt change in activation pattern and P wave upon reaching a critical rate. The latter appeared as discontinuities in the continuum of change at boundaries between ranges of rates. Subtle changes in activation characterized by point-to-point differences in activation times of greater than 2 msec accompanied changes in cycle length of 10 msec or greater. P-wave changes associated with such minor changes in activation were either slight or undetectable. Subtle changes in activation and P waves were associated with minor variations in patterns of initial depolarization. Slight differences in the relative timing or phase of O-points, as well as increasing or decreasing local conduction velocity and nonuniform patterns emanating from these locations, resulted from small cycle length changes. The site of O-point dominance did not change. Gross changes in rate or cycle length and critical crossover rates were always associated with obvious P wave changes.

Dynamic Variations in Activation —
Relation to Change in P-wave

The sudden, marked changes in activation pattern and P waves were the result of abrupt shifts in the region of earliest activation from one O-point to another, i.e. B-1, A-2, C-3 changing to A-1, B-2, C-3, or C-1, A-2, B-3, etc. This shift of the dominant early region between O-points occurred at certain critical cycle lengths or crossover rates. The particular O-point sequence, or pattern of initial excitation determined the differences in overall excitation patterns. The latter degree of change could be recognized in the P wave of a double gain and speed surface ECG (20 mm = 1 mV and speed of 50 mm/sec), while the more subtle continuum of change could not be detected without specialized amplification and recording methods. Figure 5 illustrates a correlation between the P wave in lead 2, atrial activation, and the O-point sequence, for four different states in one dog. The results in this dog were typical of those seen in most of the animals. The four states correspond to four different heart rates brought about by: 1) isoproterenol in A; 2) control state — only pentobarbital in B; 3) vagal stimulation — 15% rate reduction; 4) vagal stimulation — 30% rate reduction. Heart rate was 164, 142, 122 and 102 in A, B, C and D, respectively. As indicated in this figure, higher rates were generally associated with higher centers of early activation and slower rates with lower centers of early activation. In addition, with faster rates and higher centers of early activation, P waves were usually tall, exhibited less notching and were of short duration. In the presence of slower rates and lower centers of early activation, P waves exhibited less amplitude, increased notching, and longer duration. Thus, in most dogs the P wave was an indicator of the presence or absence of activity at higher O-points.

In several dogs with spontaneously low heart rates of 100–120 beats/min after either pentobarbital or chloralose-morphine anesthesia, the site of earliest activation was at O-point C. These findings indicate that the site of activation origin was primarily related to rate or cycle length and not to some other effect of the particular anesthetic agent.

Although there was an obligate relationship between rate change and activation change, there was no fixed or unique activation pattern for a given rate. A change in rate brought about a change in the activation maps; the altered pattern was a function of the previous pattern and the magnitude of change in cycle length of subsequent beats. Figure 6 illustrates three forms of the P wave (Pa, Pb, Pc) due to shifting of the site of earliest activation between O-points A, B and C. Figure 6A shows the change in the P wave (Pb to Pc) resulting from a shift of O-point dominance from site B to site C. Note that this change is the result of a longer interval, as the cycle length changes from 609 msec to 657 msec between the second and third beats. Figure 6B, from the same dog, shows a change in the P wave (Pc to Pa) resulting from a shift of O-point dominance from site C to A. This shift was associated with a marked change in cycle length from 685 to 342 msec. The third P wave (Pa) originated from O-point A and, although premature, was not ectopic in the usual sense. This figure emphasizes the correlation between cycle length, site of O-point dominance and P wave morphology.

Given three origin points, and that each state or pattern of O-point dominance results in a different activation sequence and new P wave, there are 13 theoretical combinations of activation, considering that they could excite in variable sequence, or two simultaneously earlier or later than the third O-point, or all three simultaneously. However, we could not evoke most of these combinations, and usually only three to five patterns were observed in one animal. The relatively small number of different activation states and related P waves may have been due to our gross methods of altering rate and perhaps because certain states were more readily evoked and also more stable.

To ascertain the effects of the interventions on local atrial conduction, independent of their effects on the pattern of initiation, the atria were paced from the O-points as well as other locations during maximum vagal stimulation or drug infusion. In comparing the
activation sequence maps during control pacing with pacing plus intervention, no differences were detected. This further substantiated that it was the altered multicentric initiation sequence produced by our interventions that determined the changes in global activation spread and resulting P wave rather than some direct effect of these perturbations on local myocardial conduction velocity.

Discussion

We were primarily interested in the dynamics, or specifically the beat-to-beat changes, in atrial activation accompanied by variations in the peaks, notches, and durations of the P waveforms. We performed no numerical analyses of P voltages, spatial orientations or quantitative comparisons of changes in these variables. We did not intend to explain quantitatively the entire voltage time course of the surface P wave. The latter would have required a thorough analysis of the time-voltage potentials over the torso as well as over the heart. Also, we were not interested in mapping activation of the shifts in the pacemaker to the extreme low atrium or AV node. In this study we were concerned with slight changes in P morphology unassociated with major changes in P axis or PR interval. Changes in the P wave associated with major variation in its axis and in the PR interval have been reported by Waldo et al. We were interested in the changes usually referred to as intranodal or shifts to locations just outside the sinus node pacemaker as described by Meek and Eyster, Sano and Iida, Eccles and Hoff, Brody et al., Van der Kooi et al., Bouman et al., West et al., Katoh, and Goldberg. Vagal stimulation was used to reduce heart rate to a
minimum of 100–120. Within this range we observed very consistent patterns characterized by early excitation at one or more sites adjacent to the SVC. When we attempted to shift the point of earliest excitation further by increasing vagal stimulation to achieve rates between 60–100, we observed less stable conditions characterized by changing rates and lower foci of excitation, presumably originating from the inferior atrium near the AV node. We did not attempt to map these latter rhythms, since they were unstable, associated with changes in PR interval and were initiated beyond our sampling electrodes.
Asymmetric Atrial Activation

Holsinger, Durrer, Goodman, Waldo, and their coworkers have shown marked asymmetry of the atrial activation. These asymmetric activation patterns have been interpreted by some as conduction in the specialized atrial pathways described by James. Spach and coworkers also demonstrated marked asymmetry of atrial activation, but they found that these patterns of asymmetry changed markedly with movement of the stimulating site, and that with different pacing sites the most rapid components of the atrial wavefronts were not consistently oriented in the same direction in relation to major atrial structures or described pathways. Interpretation of their data suggests a complex interaction between the site of origin of the atrial stimulus and the nonuniform geometry of the normal atrium. Maps of the static state sinus rhythm activation produced in this study are comparable to those reported by other investigators, with the exception of the multiple distributed areas of initiation of activation. The presence of multiple origin points differs from previous observations and is explained by the greater number of electrodes, close spatial resolution of recording points, and the improved reproducibility of results obtained by the use of fixed electrodes arranged in templates, allowing nearly identical placement on each right atrium of all dogs.

The asymmetric atrial activation patterns and conduction velocities have been related to both anisotropic atrial geometry and conduction in specialized atrial pathways. Although mapping techniques readily demonstrate specialized conduction in the ventricular endocardium, characterized by Purkinje potentials preceding myocardial potentials, rapid propagation velocities, etc., corresponding to distinct Purkinje tissue, mapping has not confirmed the presence of continuous or Purkinje-like tracts of specialized conduction in the atrium. In relation to anisotropic atrial geometry, it seems clear from this study that the superior (anterior) interatrial band region, the pectinate muscles, and the crista terminalis propagate the wavefronts faster than intervening, thin atrium. However, the exceptionally rapid velocities, greater than 1 M/sec, attributed to the crista terminalis, should be reexamined in view of the multiple, widely spaced origins of activation distributed along the terminal band. In many of the dogs with rapid rates induced by isoproterenol, O-point A became dominant and O-point C disappeared (fig. 3C). Under these conditions, propagation to the inferior right atrium became much slower and activation times to the right of the inferior vena cava were delayed by 10–20 msec. If the inferior O-point, C, represents either specialized or preferential conduction, then propagation velocities exceeding 1 M/sec occur. However, if the O-points represent multiple distributed pacemakers, then conduction velocities will be less than 1 M/sec and the range or degree of nonuniform conduction will be less than previously concluded.

Dynamics of Atrial Activation — Changes in P Wave

The changes in activation sequence and therefore the P wave were obligatory to changes in basic rate or beat-to-beat variations in cycle length. A subtle continuum of change in activation accompanied each 10-msec change in cycle length. We could not determine if even more subtle changes occurred, due to limitations in the temporal resolution of our mapping methods. Changes in surface P waves were difficult to identify at this minor level of change in cycle length and activation. Possibly, more sophisticated methods of recording and processing will reveal changes of increasing subtlety.

Shifts in the position of O-point dominance which occurred at critical cycle lengths or boundaries between rate ranges, produced marked changes in global atrial activation and easily recognizable changes in P-wave patterns. Although they changed together, cycle length and activation were not uniquely related; there was no single activation pattern associated with a specific cycle length or range of intervals. If these observations are applicable to the human atria, then an obvious change in P wave form means a shift in the location of earliest excitation between separated centers of origin. Changes from more symmetrical to more notched P-forms may indicate shift to a lower center. Brody et al. noted abrupt changes from one P-wave form to another in normal human subjects. These investigators observed two to three distinctly different P-wave patterns in some subjects and also described an even greater number of patterns in others which could not be readily categorized. Their human data suggest that our observations on atrial activation and the P wave in the dog are also applicable to humans.

Relation to Wandering Pacemaker

Many studies have reported shifts of the pacemaker to positions outside the sinus node with autonomic stimulation and drugs. In most of these studies it was not clear where the pacemaker actually shifted, since only a few points were sampled. Our studies indicate a consistent dispersion of initial activity at three separate locations, with later activity in between these sites. Shifts between these origin points would have been interpreted by us as a shift beyond the “sinus pacemaker” if only one of these early areas had been sampled. Changes in the location of earliest activity have been attributed to a “wandering pacemaker.” Our findings indicate that the early site does not drift in the sense of a gradual migration, but that the apparent wandering effect results from the shifting predominance of the area of earliest activation between the three O-points. Previous conclusions which suggest wandering of “the pacemaker” were based on the demonstration of only one early area for each dynamic state. Whether that site was actually “the pacemaker,” one of three early points, or simply the earliest recorded site, is unknown. Furthermore, many studies in which potentials have supposedly been
recorded from "the pacemaker" do not present convincing evidence that they reflect the only pacemaker. In the present study we cannot conclude that the three O-points represent pacemaker areas. However, we can speculate on the possible mechanisms and significance of these areas.

Speculation on the Mechanism on Multicentric Origin of Atrial Depolarization — Pacemaker Complex

The trifocal and widely distributed origin of the atrial depolarization wave contrasts with previous studies which demonstrate a unifocal origin. The intermediate region, O-point B, lateral to the SVC, corresponds closely to the position of the body of the sinus node. The other two points of early activation located superiorly and inferiorly lie at locations beyond the body of the sinus node. There would appear to be three possible mechanisms for this dichotomy. One explanation is three principal pacemaker centers located within a diffusely distributed pacemaker region (fig. 7A). In this model, the degree of O-point synchrony, firing sequence and changing phase of firing might be determined by a coordinating control system. Microelectrode studies have suggested an abundance of potential atrial pacemakers. Rather than numerous randomly distributed atrial pacemakers, perhaps the actual organization is a hierarchy of pacemaker centers located at specific positions within the crista terminalis. The concept of an anatomic-functional hierarchy of pacemaker centers is already recognized for the SA and AV nodes. The existence of a trifocal atrial pacemaker complex, coordinated by a feedback control system, simply extends existing concepts of pacemaker theory.

If there are three pacemaker centers, certain fundamental questions must be considered. First, how can three separate pacemakers initiate a single heartbeat? This could be due to a complex coordinating autonomic control system (the electrical brain of the heart). Neural interconnections may link all three regions to a proximal control center. This
possibility leads to another question: By what means would a neural control system effect beat-to-beat changes in the relative firing order of the three pacemaker centers? If in the control system there is constant modulation of autonomic tonus, then the O-point activation sequence reflects the instantaneous state of that tonus at the moment of the heartbeat. The tonus could be a continuously changing function in response to continuously changing afferent inputs, i.e., hemodynamic and metabolic fluctuations.

A second mechanism of trifocal atrial depolarization is one in which the sinus node impulse is conducted through three specialized pathways which connect the node to more distal atrial myocardium (fig. 7B). Our data could be explained by a threedimensional system in which the sinus node joined three pathways which were functionally insulated from the atrial myocardium, finally connecting at the locations indicated by the O-points. James has proposed specialized connections of Purkinje-like fibers which might be relevant to these observations. However, his data suggest many random connections between SA node and atrium in contrast to three distinct pathways corresponding to the positions of our O-points. In figure 7B (inset), as the pacemaker region shifts within the sinus node away from one bridge and toward another, activation would appear earlier at the connection proximal to the pacemaker and later at the connection more distal to the pacemaker. This model would explain certain observations in this study in which activation time decreased at one O-point and increased at the other O-points at the same moment.

A third possibility is a combination or hybrid of the first two models. Perhaps O-points A and B represent specialized conduction from the region of the sinus node pacemaker, and O-point C, which is farthest from the known position of the sinus node reflects a separate pacemaker center. Whatever the mechanism, these observations indicate a complex system of initiation or conduction, or both. The need for combined electrophysiologic and anatomic studies is apparent.

Possible Relation of Multicentric Organization to Heart Rate Control

The mechanism by which the adrenergic and cholinergic inputs regulate heart rate by their actions on similar cells within the sinus node pacemaker is not clear. The prevailing theory of heart rate control is that the sympathetic and parasympathetic systems exert an algebraically additive effect on a focus of pacemaker cells, and that the resulting heart rate is determined by which system predominates. The effect is mediated through acetylcholine and catecholamines by their competitive actions on the slope of diastolic depolarization of automatic cells.

Evidence by Samaan, Levy, and Katona et al. suggests that the resulting response is not due to simple competition predomination, but that complex interactions are involved in which both sympathetic and parasympathetic systems exert their effects independent of each other. If the multicentric activation represents separate sources, then the anatomic arrangement of the atrial pacemaker into three areas might have some basic functional importance. Perhaps it is not coincidental that this arrangement correlates with the different behavior of these three areas: that with faster rates, centers A or B predominate, and with slower rates, C predominates.

Our observations could be explained by a system anatomically and functionally organized, or differentiated, to regulate heart rate at two (or three) different levels. Could it be that A and B are predominantly adrenergic and C predominantly cholinergic? Also, could A and B represent different degrees of adrenergic behavior, if not further adrenergic differentiation? In this system regulation of rapid rates would depend on increasing and decreasing input and catecholamine availability to the upper adrenergic centers which would dominate the lower. Lower rates would result from decreased or inhibited adrenergic input to the upper centers and control by the lower cholinergic focus (fig. 7A). Linked to a central control system, three regions with different rate ranges might permit a wider spectrum of heart rate response and insure smooth transition between levels comparable to an automatic transmission. Also, it is possible that the three sites represent the most important atrial component of a larger, integrated system of rate regulation which includes the low atrium-coronary sinus area and AV node.

Figure 7A (inset) illustrates a model in which three pacemaker centers are coordinated by an autonomic control system with reciprocal excitation (+) and inhibition (−). In this model adrenergic centers (A and B) respond to adrenergic excitation (E) by an increase in rate or shorter beat-to-beat cycle lengths during continuous modulation. The cholinergic center (C) responds to excitation by lengthening the cycle. Reciprocal inhibitory responses are produced by both adrenergic and cholinergic stimuli (I) at the opposite centers. Inhibitory stimuli at cholinergic center (C) would produce shorter subsequent cycles at that site and a faster rate.

These observations raise several questions. The most important first step is to determine whether the three O-points represent separate pacemaker centers or the exits of three specialized conduction pathways from the sinus node. If they are found to be separate pacemakers, then electropharmacologic, electrophysiologic and anatomic studies are needed to define the pacemaker complex in more detail.

Clinical Implications of Multicentric Initiation of Depolarization

Changes in P-wave morphology during sinus arrhythmia or changes in heart rate, etc., probably represent changes in the atrial activation sequence resulting from shift of the site of earliest excitation between O-points. Also, late diastolic atrial "extrasystoles" which characteristically exhibit different P waves may actually represent atrial depolarization originating from a non-dominant O-point in contrast to some random ectopic focus.
If there are three pacemaker areas, there is an even
greater safety factor built into the initiation of the
atrial impulse. Malfunction of adrenergic mechanisms
due to autonomic or atrial disease, \( \beta \)-adrenergic
blockers, etc. could eliminate faster rate responses of the
higher centers A and B, and not terminate impulse
initiation completely. Such failure might result in
rhythms initiated from the lower, predominantly
cholinergic center, C, causing slower rates and
notched P waves such as those seen in some patients
with clinical sinus node disorders. In addition, slow
heart rates and abnormal P waves occurring after
atriotomy and correction of congenital heart defects
could represent trauma to upper centers, A and B,
with depolarizations initiated from the lower O-point,
C.\(^{26}\) Also, multiple pacemakers may form the sub-
strate for atrial parasystole and ectopic tachycardias if
the central control mechanisms become uncoor-
dinated.

If the basis for multiple origin points is specialized
conduction in three exit pathways, the safety factor for
conducting the normally initiated impulse would be
less because of the increased vulnerability of these dis-
crete connections compared to broad connections
between pacemaker and atrium. Interruption of such
paths could be important in the genesis of atrial bradyarrhythmias. Finally, if separate, discrete
pathways conduct impulses from a single pacemaker
there is a potential for dissociation of activation, cir-
cus movement, and SA reentrant tachyarrhythmias.
The basis for an association between tachy- and
bradyarrhythmias of such a substrate is apparent.

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