Demonstration of a widely distributed atrial pacemaker complex in the human heart*

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ABSTRACT Atrial depolarization was analyzed in 14 patients with the Wolff-Parkinson-White syndrome undergoing surgery to ablate accessory atrioventricular pathways associated with tachyarhythmias. Bipolar potentials were recorded simultaneously from 156 atrial epicardial electrodes arranged in three templates to fit the anterior and posterior aspects of both atria. Spontaneous or sinus rhythms were recorded, as were atrial escape rhythms after overdrive pacing at rates of 150 and 200 beats/min. Atrial activation maps revealed different patterns of impulse initiation varying from typical unifocal sinus node impulse origin, unifocal extranodal impulse origin, and multicentric impulse origin from two to four widely distributed atrial pacemaker sites. In subjects demonstrating only unifocal impulse origin during control or sinus rhythm, other widely divergent pacemaker sites were recorded in other maps during subsequent rhythms. In addition to sites located at the upper superior vena cava–right atrium junction, pacemakers also dominated sites anterior and inferior to the sinus node region during both control and escape depolarizations. Most of the subjects were found to have two or more pacemaker sites when maps of all control and postpacing conditions were analyzed. The right atrial pacemaker region encompassed a zone of 7.5 × 1.5 cm centered about the long axis of the sulcus terminalis posteriorly and the precaval band anteriorly. An unexpected finding was the participation of left atrial escape pacemakers. The functional behavior of both the control and escape pacemakers, as assessed by sinus node recovery time, was normal, indicating physiologic operation of the extranodal sites as part of an overall system of distributed pacemakers involved in the control of rate. Although functional assessment was limited in these initial patient studies, correspondence with similar observations in extensive previous canine studies supports the concept of a widely distributed atrial pacemaker complex in man.


SINCE Lewis et al.1 first demonstrated the site of earliest potential negativity on the atrial epicardium over the Keith-Flack node, a unifocal sinus origin of the atrial impulse has been the accepted theory. All electrocardiographic interpretation and electrophysiologic investigations, including extracellular mapping of atrial depolarization and intracellular microelectrode recording of pacemaker potentials, have started with this basic assumption. Although most studies have indicated that the principal atrial impulse originates from a very focal region near the head of the sinoatrial node, numerous animal studies have demonstrated pacemaker shifts within the sinoatrial node, shifts to atrial sites outside the sinoatrial node, and normal atrial pacemaker activity with removal of the sinoatrial node.2–22 However, there has been little direct evidence of a consistent set of pacemakers outside the sinoatrial and atrioventricular nodes. Thus, the present day concept of pacemaker hierarchy is the sinoatrial node and the atrioventricular node, followed by the specialized ventricular conduction system. All other extranodal atrial pacemaker sites have been considered to be subsidiary and inconsistent or ectopic and abnormal.23

Although collisions between sinoatrial and atrioventricular node wavefronts are recognized, the atrial impulse is believed to originate unifocally and fusions between two or more atrial pacemakers firing simultaneously are seldom considered. Even though there has been little direct evidence to implicate anything other than a unifocal sinoatrial node origin of the normal atrial impulse in man, there has been considerable indirect evidence suggestive of a different mechanism con-
tained in the electrocardiogram and characterized by changes in the P wave.24

Canine studies in which potentials have been recorded from multiple electrodes simultaneously have revealed an extensive pacemaker complex in which sites of atrial impulse origin are widely distributed over the right atrium.25–30 These studies have also demonstrated multicentric impulse origin in which atrial depolarization waves can originate from up to three widely separate sites simultaneously, and frequent exchange of dominance among the multiple pacemakers coinciding with changes in heart rate and beat-to-beat cycle length. These changes in initiating conditions produce changes in the pattern of global atrial depolarization, which are reflected in differences in the P waves of the electrocardiogram.

Using atrial mapping methods similar to those previously developed for the canine studies,28 we recorded the normal atrial activation dynamics from the exposed human heart at the time of surgery. The data obtained during spontaneous atrial rhythms and after overdrive atrial pacing demonstrate that atrial electogenesis in humans is also complex and results from an extensively distributed system of atrial pacemakers. This system extends widely over the right atrium along the crista terminalis, and there is also limited participation of left atrial foci. In addition, pacemakers distant to the sinoatrial node typically dominate junctional pacemakers. This report represents the first demonstration of the existence of a widely distributed pacemaker complex in man. The presence of distributed electogenesis may help to clarify many experimental and clinical observations that are inconsistent with the concept of a stable, unifocal atrial pacemaker.

Methods

Fourteen patients with the Wolff-Parkinson-White (WPW) syndrome and supraventricular tachycardias undergoing surgery to ablate accessory atrioventricular pathways were studied. During arrhythmia-free periods, these patients demonstrated normal sinus rhythm and no evidence of atrial bradyarrhythmias. The patients ranged in age from 15 to 36 years. Four patients had mitral valve prolapse without significant mitral regurgitation documented by two-dimensional echocardiography. Five patients demonstrated spontaneous atrial fibrillation and sustained atrial fibrillation was inducible in 11 patients during the preoperative electrophysiologic study. There was no evidence, clinically or during electrophysiologic testing, of sinoatrial node dysfunction in any of the patients. There was no evidence of any other cardiac pathology. All mapping studies were performed in conjunction with clinical atrial and ventricular mapping during sinus rhythm, right and left atrial pacing, ventricular pacing, and induced supraventricular tachycardias. All patients gave informed consent. In addition, the protocol used in this investigation was approved by the Washington University Committee on Human Studies.

After placing the venous and arterial cannulas, and before instituting cardiopulmonary bypass, three flexible templates, formed to fit the specific atrial structures and containing a total of 156 bipolar pairs of electrodes, were applied to the epicardial surfaces of the posterior right and left atrium and the anterior right and left atrium through the transverse sinus. The electrode-containing templates were held in place by sutures at their corners and further supported by sponge packing where necessary to ensure good electrical contact. The templates covered an area of 6.5 × 9 cm on the posterior right atrium, 4 × 11 cm on the posterior left atrium, and 4 × 9.5 cm on the anterior right and left atria. The smallest distance between recording sites along the sulcus terminalis was 5 mm. The largest distance between sites over the remainder of the two atria was 10 mm (figure 1). The distance between two electrodes of a bipolar pair was 1 mm. Each electrode was composed of 0.005 inch diameter solid silver wire insulated with 0.0015 inch Teflon coating (Medwire, Mt. Vernon, NY). Sheets of silicone rubber (0.5 mm thick) were preshaped to conform to atrial structures and imprinted with a grid. To create a bipolar pair, the silver wires were looped through the sheet at grid crossing points, exposing approximately a 1 mm surface of each wire. A liquid silicone rubber solution was applied to the back surfaces of each template to achieve fixation between the electrode wires and templates. The individual wires were coated and attached to connectors. Additional bipolar electrode plaques were sutured to both right and left atrial appendages for pacing. Figure 1 displays the atria cut along the entire outer perimeter, detached from the septum anteriorly with the anterior aspect unfolded and rotated superiority. This view retains left-to-right orientation but rotates the

![FIGURE 1. Atrial anatomy and electrode locations. Both anterior (above) and posterior (below) aspect of the atria are shown. The anterior aspect has been pivoted upward about the axis drawn through the SVC after cutting the atria along its outer margins. Note the higher density of electrodes in the right atrium along the sulcus terminalis. MV = orifice of mitral valve; TV = orifice of tricuspid valve; BB = Bachmann's bundle; PB = precaval bundle; LAA and RAA = left and right atrial appendages; IVC = inferior vena cava; PV = pulmonary veins; ST = sulcus terminalis. The vertical lines to the right of the anterior and posterior asterisks indicate the position of the atrial septum.](image-url)
inferior margin of the anterior atria by 180 degrees (superiorly) away from the posterior atria. In addition, in the display, the structures are further flattened so that the exact positions of the electrode grids can be visualized. This distorts and enlarges the posterior atrial surface more than the anterior surface because of its greater curvature. Thus, it should be noted that activation waves moving upward in the anterior atrial diagram are actually moving inferiorly. In figure 2, the computer display of the activation times on the schematic posterior atrium is illustrated along with the lead aVF electrocardiogram and selective electrograms.

All bipolar potentials were recorded simultaneously with an automated cardiac mapping system previously described by Witkowski and Corg.31 The signals were recorded at a frequency response between 40 and 500 Hz. The cardiac signals were simultaneously recorded with surface electrocardiographic (ECG) leads I, aVF, and RV5. Each of the signals was converted at a 2 kHz rate at each amplifier. A 12-bit word was presented to the output of each amplifier analog-to-digital converter and stored in tristate memory. The processed parallel signal from the data acquisition system was then converted from parallel to serial and transmitted via a fiber optic transmission system to the computer facility. The signals were then converted back from serial to parallel and stored on a digital tape recorder along with three surface ECG leads and voice information. A peak criterion algorithm as described by Witkowski and Corg et al.31 was used for determining activation times and refined according to investigator logic (figure 2). A DEC PDP 11/34 digital computer interfaced with a video terminal, a printer, a color graphics display system, and specially designed software was used to create the map images. The maps were displayed with the activation times projected onto each electrode position. The isochronous lines were then drawn by hand. Final maps were edited and confirmed by two observers.

The recording time for each patient was limited to a strict protocol and integrated with the clinical-diagnostic mapping and stimulation methods. For each patient, at least one prolonged period of spontaneous atrial rhythm (sinus rhythm) was recorded. Additionally, activation was recorded during and immediately after right atrial and then left atrial pacing at three different cycle lengths (500, 400, 300 msec). The period of recording was extended beyond the duration of overdrive stimulation so that the atrial escape mechanisms could be mapped for several return cycles and sinus node recovery time (SNRT) could be determined.

**Definition of terms.** Although most atrial myocardium, intact or isolated, may demonstrate automatic activity under certain conditions, we refer to a subset of principal component atrial pacemakers that function under physiologic conditions to initiate the normal atrial or sinus rhythms.

**Distribution**

1. The atrial pacemaker complex (APMC) is used to indicate an entire system of right atrial pacemakers, some of which are outside the sinoatrial node (extranodal).

2. Anatomically, the component pacemakers are distributed within a 1.5 x 7 cm corridor beginning at the anterior superior vena cava-right atrium (SVC-RA) junction overlying the precaval bundle, and extending posteriorly along the descending sulcus (crista) terminalis to the level of the inferior vena cava (IVC).

3. The multiple sites of origin are typically separated by distances equal to or greater than 1 cm. Spaces intermediate between multiple points of earliest activation demonstrate zones or bridges of later activation surrounding all earlier sites, indicating multiple wavefronts expanding from separate sources and merging.

**Function**

1. Unifocal origin (UFO): The pacemaker sites may each dominate separately such that one site unifocally initiates one depolarization wave, or over several minutes, multiple unifocal

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**FIGURE 2.** Computer display. Left, The computer display of the activation times at the location of each electrode on the posterior atrium. Top right, A segment of the electrocardiogram in lead aVF. The box around the one waveform is the 248 msec window analyzed to make the activation map on the left. Selected electrograms are shown in the bottom right. The window of data is 248 msec and corresponds to the window of data on the above electrocardiogram. The number in the upper left corner of each electrogram corresponds to the channel number. The small number is the calibration and corresponds to the dark thick vertical line before the start of the electrogram tracing. On each electrogram, the thin vertical line represents the computer-picked activation time. A line points to the circled time on the posterior atrium corresponding to each of the illustrated electrograms. All times are adjusted to the earliest time, which is designated as 0 msec.
sites may sequentially dominate as the pacemaker site shifts with changing autonomic conditions and heart rate.

(2) Multicentric origin (MCO): Under certain conditions, multiple pacemakers (two to four) may simultaneously depolarize, giving rise to multiple wavefronts that coalesce in the right atrium within the first 10 to 15 msec.

(3) Under other conditions, MCO can also occur when multiple pacemakers (two to four) depolarize asynchronously, such that one or more are out of phase and lag an earlier site by 1 to 5 msec.

(4) Pacemakers that lag by more than the conduction time between two sites will be passively depolarized and not result in the initiation of a separate wavefront.

Multiple pacemaker sites. Patients exhibiting different unifocal sites of impulse origin separated by a distance of 1 cm or more in different maps were considered to have multiple pacemaker sites.

Subsidiary atrial pacemakers. These are not part of the pacemaker complex as defined above. They occur outside the APMC proper, are normally suppressed by the APMC, and operate only under unusual conditions; under experimental conditions, this typically means destruction or removal of multiple components of the pacemaker complex or compromise of its circulatory supply.

Results

Spontaneous atrial rhythms (sinus rhythm). Figure 3 illustrates the spontaneous or sinus rhythm in four of the 14 patients. The first 10 msec of depolarization are in color to emphasize the sites of impulse origin. A typical example of sinus rhythm is illustrated in panel A. Note that activation originates posteriorly and medi-
al to the sulcus terminalis at the SVC-RA junction 10 to 15 mm below the cavoappendicular junction or crest of the right atrium. The region of early depolarization is localized or focused and there are no distinct areas of early depolarization. Panel B illustrates early depolarization in another patient originating in the anterior atrium at its junction with the SVC. Once again, note that the anterior area depolarized by 10 msec is quite localized. However, there is a second site of depolarization located at the posterior SVC-RA junction. In panel C, activation originates inferiorly at the posterior IVC-RA junction in a third patient. This site is approximately 4 cm below the origin points noted in the other two patients (panels A and B). Also, unlike the first two subjects, activation appears more nonuniform with marked superior elongation of the 10 msec wavefront. Note that a region of later activation is inter-
posed between earlier times at the superior and inferior limits of this 10 msec isochronous zone. The surface ECG P wave morphology in each of these patients is quite different, reflecting the different atrial depolarization patterns that in turn are determined by the different initial sites of activation.

The maps shown in figure 3, D, represent a more accentuated form of MCO. There are three primary sites of origin, one anteriorly and two posteriorly. The anterior site is located 20 mm from the upper posterior site and 16 mm separates the two posterior sites. Addi-
tionally, there is a fourth site delayed by 5 msec and located within the intercaval region in the posterior right atrium. It should be emphasized that this activation pattern repeats with each cycle, and that the stabili-
ity of this pattern is associated with a consistent morphology of the ECG P wave for multiple successive cycles. In comparison with the maps illustrated in the previous panels, the map in panel D exhibits a more extensive area of right atrial depolarization by 10 msec that is 7.5 cm in length as measured from the anterior and posterior limits of the wavefront. This is approximately three times the area of the 10 msec wavefront (2.5 cm) shown in panel A. Panel A represents an example of unifocal impulse origin, whereas panels B, C, and D represent examples of multicentric impulse origin as previously defined. Panel D represents the most conspicuous of the three examples of multicentric impulse origin.

Atrial escape activation. The site of impulse origin of escape pacemakers after overdrive suppression is shown in four examples in figure 4. Panels A and B show two different escape depolarizations occurring after two different rates of overdrive pacing (150 and 200 beats/min in A and B, respectively) in the same patient whose map of spontaneous depolarization is shown in figure 3, C. Note that in contrast to the inferior location of impulse origin in figure 3, C, the escape after overdrive suppression at the rate of 150 beats/min (figure 4, A) occurs from a higher positioned pacemaker. The distance between the two earliest areas of depolarization in the two maps (figures 3, C, and 4, A) is 4 cm. In figure 4, B, the map of the first return cycle after overdrive stimulation at the faster rate of 200 beats/min reveals the simultaneous firing of both of the widely separated pacemaker sites that individually dominated in the maps from this patient in figures 3, C, and 4, A. Panels C and D of figure 4 illustrate, respectively, the first and second successive return depolarizations after overdrive pacing at a rate of 200 beats/min in the same patient whose map of spontaneous rhythm is shown in figure 3, D. The first return beat in figure 4, C, demonstrates distributed impulse origin as does the control map (figure 3, D) at both superior and inferior sites. However, in contrast to the control rhythm, the anterior site is 5 msec earlier than the two posterior sites. In the second return beat (figure 4, D), the site of earliest activation occurs in the midposterior right atrium, corresponding to the lower site that activated at 5 msec in panel C. In the absence
FIGURE 3. Control or “sinus” rhythms in four patients. The first 10 msec of atrial depolarization are in color (shaded) to emphasize the sites of impulse origin. Note the different patterns of impulse origin and how they affect global atrial activation and the morphology of the P wave in lead aVF below each panel. Typical unifocal sinus node impulse origin is illustrated in A. Different forms of multifocal impulse origin are illustrated in B, C, and D. Note the widely distributed pattern of impulse origin in D, with four different pacemaker sites participating.
FIGURE 4. Atrial escape rhythms. A and B, Patterns of impulse origin and global atrial depolarization associated with the first escape depolarization after termination of pacing at 150 beats/min in A and the second escape depolarization after terminating pacing at 200 beats/min in B, in the patient whose control rhythm is shown in figure 3, C. Note that the first escape depolarization in this patient occurs from a more superiorly positioned pacemaker that completely dominates the two lower sites that initiated control rhythm (compare figure 3, C, and A here). B, Both the low and higher pacemaker sites simultaneously initiate depolarization in the second escape cycle. Also note the difference in P wave configurations associated with the different patterns of global atrial activation in comparing figure 3, C, with A and B here. C and D, The first and second escape depolarizations, respectively, after termination of pacing at 200 beats/min in the patient whose control rhythm is shown in figure 3, D. In C, note that the anterior pacemaker site is 5 msec earlier than the posterior pacemaker sites, which depolarized earlier during control rhythm (compare figures 3, D, and C here). In D, note that the lowest positioned pacemaker in the second escape depolarization dominates all other sites, which were earlier in the control rhythm (figure 3, D). Again, note the differences in the P wave recorded from aVF associated with each different pattern of impulse origin and the resulting change in global atrial depolarization.
of earlier activation in the superior right atrium (figure 4, C), the lower posterior site now dominates. This is a typical example of the exchange of pacemaker dominance that is representative of the dynamics observed in this study. In comparing the maps of the individual patients in figures 3 and 4, also note the changes in the P waves of lead aVF, which reflect the changes in atrial activation sequences resulting from the different sites of impulse initiation.

**Sinus arrhythmia.** In several patients, maps were obtained during sinus arrhythmias in which there were spontaneous cycle-to-cycle changes in ECG P waves. Figure 5, A, illustrates ECG lead aVF, and two different conditions of atrial impulse initiation are illustrated in panels A and B, respectively. Panel A corresponds to the tall P wave and preceding shorter cycle and panel B corresponds to the lower amplitude, more notched P wave and longer cycle. Note that in panel A the site of earliest atrial depolarization is located anteriorly at the SVC-RA junction. However, a second site depolarizing 5 msec later is located along the posterior SVC. In panel B, the site of earliest impulse origin has shifted to the posterior site. This represents a typical exchange of dominance among two pacemaker regions separated by 2.5 cm, both of which are contributing to impulse origin.

**Left atrial escape pacemakers.** In addition to widely distributed sites of impulse initiation in the right atrium, initiation of atrial depolarization was also noted from the left atrium during escape rhythms after overdrive pacing. Evidence of left atrial pacemakers in this study was restricted to a region beneath the left inferior pulmonary vein. Figure 6, A, illustrates spontaneous (sinus) rhythm, and the first (panel B) and second (panel C) return depolarizations after overdrive pacing at a rate of 150 beats/min, all in the same patient. In figure 6, A, during control rhythm, note the superior location of the pacemaker at the cavoappendicular

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**FIGURE 5.** Shifting pacemaker dominance reflected in changes in P wave. The electrocardiogram recorded in lead aVF is shown above. A and B indicate two different P wave morphologies. The sites of impulse origin and the resulting patterns of global atrial activation associated with each P wave are shown in A and B below. Two competing pacemaker sites are shown in A. The anterior site depolarizes 5 msec before the posterior site. The next cycle, shown in B, demonstrates dominance of the posterior pacemaker site with passive depolarization of the previously dominant anterior site. This is a typical example of the exchange of dominance between competing pacemakers, which results in changing P wave configurations in "sinus arrhythmia" and other unstable atrial rhythms. Although the P wave morphology reflects the differences in global atrial depolarization, this pattern is the result of different initiating conditions. See text.
FIGURE 6. Left atrial escape rhythms. A, The control or sinus rhythm; B, C, and D, various escape depolarization patterns for the same patient. D, A left atrial escape rhythm in which the pacemaker site adjacent to the left inferior pulmonary vein dominates as all right atrial pacemakers are passively depolarized by the earlier left atrial wavefront. B and C, Two different patterns of biatrial fusion in which the left atrial pacemaker escapes earlier in B and the sinus node pacemaker escapes earlier in C. The different patterns of global atrial depolarization resulting from the different initiating conditions result in different P wave configurations recorded from lead aVF. In B and C, the asterisks identify the location of the nondominant or later depolarizing pacemaker.

In contrast, note the left atrial position of the pacemaker in the first return beat (figure 6, B) and the high right atrial site of the predominant pacemaker during the second return depolarization (figure 6, C). Figure 6, D, illustrates a left atrial escape depolarization for the second return beat after right atrial pacing at a rate of 200 beats/min. The delayed activation of the right atrium shown in this map is consistent with predominant left-to-right spread of atrial wavefront. The escape depolarization shown in figure 6, B, represents a fusion between the two pacemaker sites, the predominant or earlier site in the left atrium followed 40 msec later by escape of the right atrial pacemaker. Evidence for the delayed right atrial pacemaker in panel B is derived from the pattern and earlier activation times of the upper right atrial wavefront, which is shown to approach and then merge with the left atrial wavefront (compare with panel D). In panel C, although the dominant pacemaker is in the right atrium, by comparing the pattern and times of left atrial activation in this map with those in the map of sinus rhythm in panel A, it can be seen that this escape also represents a fusion between right and left atrial foci. The points of left atrial impulse origin encountered in this series are also depicted in figure 7, which demonstrates all of the locations in both right and left atrium where impulses originated. All atrial escape rhythms were associated with the initiation of atrial activation preceding the onset of the P wave in the electrocardiogram, which in turn preceded the onset of QRS. Atrioventricular junctional rhythms were infrequent and occurred in six of 83 maps (7%) of escape depolarizations, and were identified by the close timing of atrial activation in relation to QRS and sites of earliest epicardial atrial depolarization located inferiorly and adjacent to the septum. Five of these were recorded in
one patient and occurred after atrial pacing as a parasympathetic rhythm where the atrioventricular junction synchronized with an atrial pacemaker. Another occurred as an isolated atrioventricular junctional rhythm on termination of ventricular pacing in a different patient.

**Spatial distribution and localization of pacemakers.** The location of all positions where earliest activation was recorded in a map are plotted in figure 7. This figure is intended to summarize only the extent of distribution of the atrial pacemakers and not the relative incidence of impulse origin at each location. Note that spontaneous rhythms (filled circles) originate from a region of 1.5 cm (width) × 7.5 cm (length) along the SVC-RA junction, extending from the anterior aspect, posteriorly to the inferior limbus of the SVC. The distribution of the escape pacemakers (open circles) approximates the zone of spontaneous rhythm sites, and also involves the left atrium.

**Global spread of atrial activation — its relation to sites of initiation.** The initial conditions of the number and locations of sites of impulse origin significantly influenced the pattern and timing of global atrial activation. Differences in this pattern, and in particular the sites of latest atrial activation, could be directly related to differences in the patterns of impulse initiation. As can be seen in figure 3, A, with unifocal impulse origin from the region of the sinoatrial node, activation proceeded from this solitary site of initiation as two wavefronts: one wavefront propagated rapidly inferiorly along the crista (sulcus) terminalis of the posterior right atrium through the intercaval region to the posterior left atrium, and the other propagated superiorly, anteriorly, and right to left over Bachmann’s bundle to reach the left atrium. The left atrial appendage was activated exclusively via this anterior wavefront, which ultimately propagated onto the posterior left atrial appendage. Subsequently the inferior body of the left atrium was activated by the two opposing and merging wavefronts; one from the left atrial appendage moving inferiorly and the other reaching the left atrium below the pulmonary veins through the intercaval region of the right atrium. The latest region to be activated was a small zone on the posterior left atrial surface beneath the left inferior pulmonary vein. As can be seen from the diagram, total atrial activation lasted 109 msec. In comparison with the subsequent maps in figure 3, B, C, and D, in panel A a large zone of the left atrium with a perimeter of 6 cm remained to be activated at 100 msec. As a result of the single site of impulse origin in this patient, total right atrial activation time was 57 msec. Since left atrial activation ended at 110 msec, this resulted in an activation phase difference of 53 msec between the two atria.

In figure 3, B, as a result of the early anterior site of impulse origin, the left atrial wavefront reached the atrial appendage 20 msec earlier than in the map of the previous subject (panel A). Even so, there was a very similar pattern of anterior-to-posterior activation of the left atrial appendage. Activation in the posterior right atrium proceeded from a second focus in the posterior right atrium that began coincident with the anterior wavefront. This wavefront again spread inferiorly across the intercaval band and into the inferior left atrium. Thus, as in the previous example, latest activation was on the posteroinferior surface of the left atrium as the two wavefronts merged. However, in contrast to the example illustrated in figure 3, A, note the relatively small (25 mm perimeter) zone of unactivated left atrium at 90 msec. Also note that there is less disparity in total right vs left atrial activation time. Since the latest activation of the inferior right atrium was 65 msec, there was only a 25 msec right atrial–left atrial time difference, or approximately half the difference recorded in panel A. In figure 3, C, activation of the posterior right atrium is quite different from that
shown in the previous two panels. The wavefront proceeds from inferior to superior in the right atrium, and the anterior atrial structures, including Bachmann's bundle are depolarized predominantly from the emergence of the septal wavefront inferiorly at 30 msec. This anterior and septally transmitted wavefront merges at the cavoappendicular junction, with the posterior wavefront propagating over the epicardial surface from the inferior right atrium. Similar to the previous two examples (figure 3, A and B), the left atrium is activated by merging anterior and posterior wavefronts. However, in contrast to the previous two examples, the two wavefronts meet at the left atrial appendage, with the latest activation time at 90 msec occurring in three separate islands. The most frequent site of latest atrial depolarization was in the posteriorinferior left atrium beneath the left inferior pulmonary vein, as illustrated in figure 3, A, B, and D. This latest area of activation represented the most frequent site of convergence of the two wavefronts.

Rapid dispersion of atrial wavefront. A by-product of multicentric origin is rapid dissemination of atrial depolarization wavefronts. It is clear from analysis of the maps of figures 3 to 5 that MCO results in a more rapid dispersion of early right atrial wavefronts than unifocal impulse origin. In figure 3, A, in which there is UFO, note that the total activation time is 110 msec and also that the 10 msec wavefront is relatively focused, with a length of only 25 mm. In comparison with the patterns of depolarization in panels A, B, and C of figure 3, note the effect of the four separate sites of impulse origin in panel D. The total activation time is only 90 msec due to the greater degree of left atrial activation by the anterior wavefront. Also, note the elongated distribution of the 10 msec wavefront in the right atrium with a length of 75 mm between its anterior and posterior limits. This represents early depolarization of an area three times that resulting from UFO in panel A. This is evidence that the rapid dissemination of the early right atrial wavefronts is not due to specialized conduction but to distributed initiation.

Recovery times of spontaneous (sinus) and escape pacemakers. An analysis of the function of both the control and escape atrial pacemakers is presented in figure 8. In this figure, pacemaker recovery time on the ordinate is plotted against spontaneous cycle length. The dashes indicate the line of normality derived from studies by Mandel et al.32 and Josephson and Seides.33 Pacemakers that return to the control site after termination of overdrive stimulation (group I) are indicated by the filled circles. This is compared with pacemakers that did not return to the control position after overdrive suppression (group II), which are represented by the open circles. There were 27 examples in group I and 17 in group II. Note that escape pacemakers returning to the control site (group I) fall within a narrow range (r = .89) compared with escape pacemakers that do not return to the control site (group II), which are more scattered (r = .55). The greater temporal scatter correlates with the greater spatial scatter of the escape pacemakers shown in figure 7. The regression line of group II indicates that escape pacemakers occurring at a site other than the control pacemaker site exhibited a shorter recovery time. All of the escape pacemakers from both groups fell within the normal range for sinoatrial node recovery time, with no times greater than 1.2 sec.32,33

Incidence of MCO and change in pacemaker conditions. Atrial activation maps were recorded during spontaneous or control rhythms and after overdrive stimulation of the atria. Thus, maps were obtained for control (sinus) rhythm, for the first return cycle after overdrive suppression of spontaneous rhythm, and also for later return cycles (second, third, fourth, etc.). In some patients, it was possible to record more than one period of spontaneous rhythm and in others it was possible to record escape rhythms after multiple episodes of overdrive pacing and suppression of spontaneous rhythms. These results are presented in table 1. All rhythms, including both control and escape cycles, were analyzed for the incidence of UFO vs MCO and for recovery times. In addition, the first return cycle as well as later return cycles (second, third, etc.) were analyzed to determine whether the location of the pacemakers returned to the control (pacemaker) sites or to other
(pacemaker) sites that were different from the control conditions. As can be derived from the table, the mean cycle length during control rhythm was 707 msec. During control or "sinus" rhythm seven of the 14 patients (50%) demonstrated multicentric impulse origin.

The first return cycles after overdrive pacing were examined to find how frequently pacemakers during the escape cycles failed to return to their original sites present during the control rhythms. In 18 of 46 (39%) such maps, new pacemaker conditions were present in the first return cycle that were not in the spontaneous cycle. Thus, pacemaker conditions of the first return cycle were the same as those during the spontaneous cycles in 61% of the maps. Twenty-three of the 46 maps of the first return cycle exhibited multicentric impulse origin, an incidence of 50%. The difference in the mean cycle lengths of pacemakers returning to the control sites (829 msec) and the other sites (739 msec) was significant (p < .05) for the first return cycle.

For later return cycles, the total number analyzed represents all combinations of a single cycle being recorded multiple times or multiple successive cycles being recorded once. Of all of the maps analyzed for return cycles later than the first (i.e., second, third, fourth, etc.), 15 of 37 maps (40%) demonstrated pacemaker locations different from those present during the control rhythm. It was not possible to examine enough return cycles to determine how soon control pacemaker conditions were reestablished at the original sites. The difference in the mean cycle lengths for the later return beats in which the pacemakers returned to control sites was 776 msec, as compared with 728 msec for pacemakers not returning to control conditions (not significant). Multicentric impulse origin was present in 20 of the 37 maps (54%) obtained for the later return cycles. An analysis of all the maps for all conditions for all of the patients indicated an overall incidence of multicentric impulse origin of 52%.

The last column in table 1 indicates the number of pacemaker sites observed in each patient from analysis of all maps recorded for that individual. Twelve of the 14 subjects demonstrated two or more widely separated pacemaker sites. In the two patients exhibiting only one pacemaker site, only one map was available for analysis in each case. This was due either to the time constraints and the inability to obtain multiple maps of sinus rhythm or inability to carry out the stimulation protocol, which was at the discretion of the surgeon. Thus, one pacemaker site was recorded in two patients, two pacemaker sites in five patients, three pacemaker sites in five patients, and four pacemaker sites in two patients.

Discussion

Since the preexcitation syndrome represents a form of congenital heart disease and because four patients exhibited spontaneous atrial fibrillation, the question arises as to whether the data obtained represent normal or abnormal pacemaker activity. This question cannot be answered without similar activation data from normal human subjects for comparison. However, the marked similarity to the data obtained in the normal canine atria supports this assumption.

The incidence of change in pacemaker conditions after overdrive pacing and the frequency of multicentric impulse origin were derived from the available data on the 14 patients. The data were affected by the different number of maps and pacemaker conditions obtained for each patient. For example, in patient 3, it was possible to record only one first return cycle, whereas in patients 5, 6, and 10 it was possible to record up to six postpacing escape rhythms. The data were therefore influenced by these individual differences in sampling. However, there is considerable internal consistency of the data that can be seen by comparing the incidence of MCO during the control (53%), first return (50%), and later return cycles (54%), as well as the overall incidence (52%). Therefore, it would appear that distributed impulse initiation in the atrium is relatively frequent, occurring approximately 50% of the time. Additionally, the incidence of change in pacemaker conditions after overdrive stimulation (39% for first return cycles and 41% for later return cycles) indicates that this is a relatively common event.

Patients with multiple pacemaker sites may exhibit either UFO or MCO in an individual map or during a period of stable rhythm. Whether or not a patient demonstrates UFO or MCO in an individual map, the majority of our patients (12 of 14) exhibited multiple pacemaker sites when all of their maps were analyzed. However, in the two patients in whom only one pacemaker site was identified, only one map was recorded in each. Had time and the clinical situations permitted, additional maps may have demonstrated pacemaker sites in these individuals. In a patient with widely separated pacemaker sites, the presence of UFO vs MCO is determined by the phase relations between two or more sites, the distances and conduction velocities (conduction time) between sites. The greater the phase difference and the closer the distance between two sites, the more likely UFO will be recorded and vice versa. Most of the patients demonstrated multiple pacemaker sites, regardless of whether MCO was present in an individual map. MCO should have been recorded eventually in all patients had we had the oppor-
tunity to map under different autonomic stress. Therefore, MCO-UFO represent the conditions of initiation at one moment in time and may not be representative of the total number of separate pacemaker sites present in an individual.

Although this study focuses on the widespread system of atrial pacemakers, it is not inconsistent with studies concerned with the interactions among multiple closely positioned pacemaker cells within a single pacemaker center. The difference is in the mechanism of coordination. As pointed out by Michaels et al., closely positioned and electrotonically coupled pacemaker cells interact through a mutual entrainment process, whereas the widely distributed pacemaker complex may require a different mechanism of coordination and control (another level).

The agreement of recovery times of all pacemakers mapped in this study with those previously reported is evidence of a normal or physiologic operation of all pacemakers observed, and that the extranodal sites do not represent extraordinary outliers associated with random or inconsistent events. The conclusion from these data is that these extranodal sites represent normal pacemakers.

It is of historical interest that pacemakers outside the sinus node were predicted by investigators before the description of the sinoatrial node by Keith and Flack. Remak described atrial ganglia at the anterior superior RA-SVC junction, which he predicted would be a site of atrial impulse origin. This position coincides with the anterior location of the pacemaker described both in our patients and in the canine studies. In addition, Fredericq described an “ultimum moriens” atrial pacemaker located in the inferior right atrium and this coincides with the intercaval position of right atrial pacemakers recorded in our patients and in most of our animal studies in which either cholinergic stimulation or adrenergic blockade was used to reveal the pacemaker.

The original atrial activation studies by Lewis et al. have had a profound influence on recognition of the site of impulse origin. The conclusion of Lewis that there is a UFO of the atrial impulse from the region of the sinoatrial node has remained unchallenged until recently. He found a unifocal origin of atrial depolarization characterized by a single site of early negativity located at the cavoappendicular junction and correlated that position histologically with the rostral portion or body of the sinoatrial node. However, these conclusions were based on findings in only seven of 10 dogs. In three of the animals, he was unable to consistently locate the position of the atrial pacemaker and was

### TABLE 1

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Control cycle</th>
<th>First return cycle</th>
<th>Later return cycles</th>
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<tr>
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<td>CL</td>
<td>UFO</td>
<td>MCO</td>
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<tr>
<td>1</td>
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<td>0</td>
</tr>
<tr>
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</tr>
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<td>652</td>
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<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>8</td>
<td>46</td>
</tr>
</tbody>
</table>

Mean ± SD | 47 | 53 | 60 | 39 | 50 | 50 | 59 | 41

CL = cycle length; PM = pacemaker; av = average.

*CL and PM spontaneously changed during control rhythm.

p<.05

NS
TABLE 1  
(Continued)

<table>
<thead>
<tr>
<th>Later return cycles</th>
<th>Subtotal</th>
<th>No. of different Sites</th>
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<tr>
<td></td>
<td>UFO MCO</td>
<td>UFO MCO Sites</td>
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<tr>
<td>CL (av)</td>
<td></td>
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<tr>
<td>___</td>
<td>___</td>
<td>___</td>
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<td>1</td>
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<td>4 0</td>
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<td>20</td>
<td>47 51</td>
</tr>
<tr>
<td>46</td>
<td>54</td>
<td>48 52</td>
</tr>
</tbody>
</table>

728 ± 185

unable to determine the origin point because it was not stable. It is also of interest that Wybauw\(^\text{38}\) located the site of impulse origin in dogs at a site lower than that described by Lewis. Most subsequent studies on canine atrial activation confirmed the original conclusions of Lewis, describing impulse origin occurring near the superior margin of the cavoappendicular junction. However, in certain studies there have been isolated examples of pacemakers outside the region of the superior cavoappendicular junction, but these have not been observed consistently or received widespread attention.\(^\text{10-12}\) Additionally, studies in smaller animal species, such as the rabbit, have demonstrated small displacements of the pacemaker within the sinoatrial node with autonomic manipulations (vagal stimulation, etc.), but these shifts were over small distances of 1 to 4 mm.\(^\text{2-6, 8, 9}\)

In canine studies, we previously described a widely distributed atrial pacemaker complex in which impulses originated from a number of corresponding sites spread over a 5 × 1.5 cm zone extending from the anterior superior right atrium posteriorly and inferiorly along the sulcus terminalis.\(^\text{25, 26}\) Subsequently, we were able to document a close correlation between spatial position and function (rate or cycle length).\(^\text{27}\) This association implicates a system of spatially distributed atrial pacemakers functionally differentiated such that faster rates are initiated by the more superiorly positioned pacemakers and slower rates are initiated by more inferiorly positioned sites. Of singular consequence at intermediate rates, atrial impulses were noted to originate from two to three sites simultaneously, giving rise to multiple merging wavefronts and resulting in widespread dissemination of early depolarization in the right atrium.

Previous human atrial activation studies during spontaneous rhythms have been limited to patients in which nonsimultaneous sampling techniques were used. Studies by Durrer,\(^\text{39}\) Brusca,\(^\text{40}\) and Spach\(^\text{41}\) and their colleagues all described unifocal atrial impulse origin at the superior cavoappendicular junction. Thus, the concept of an extremely stable UFO of the atrial depolarization wave has become firmly ingrained.

Since our observations on human atrial activation differ from those previously published, some explanations are indicated. First, because serial or nonsimultaneous recordings using smaller electrode numbers cannot overcome the spatial and temporal complexities associated with a distributed and dynamically changing system of atrial pacemakers, previous studies using these methods would not be expected to reveal them. Because of the high density of electrodes and simultaneous recording of all potentials, dynamic or unstable pacemaker conditions characterized by abrupt changes in pacemaker location can be seen. Second, because the electrodes are permanently fixed in a defined grid and are applied in the same way in each patient to conform to the atrial structures with use of consistent anatomic reference points, patient-to-patient comparisons are possible and individual differences as well as common patterns can be appreciated.

The present data in human subjects confirm the existence of an atrial pacemaker complex in man. The dimensions of this distribution of right atrial pacemakers cover an area of 7.5 cm in length by 1.5 cm in width. This contrasts with the reported size of the human sinoatrial node, which varies between 4 and 20 mm in length.\(^\text{23, 42-44}\) The human data are similar to the canine observations with respect to the general distribution of pacemakers along the sulcus terminalis. As in the dog, pacemakers were noted anteriorly at the SVC-RA junction. Endocardially, this is the location of the precaval bundle, which is the anterior continuation of the crista terminalis.\(^\text{45}\) Although inferior pacemaker locations were observed in these patients, they were not seen with the same frequency of caudal sites as in the previous canine studies. This difference was related to the differences in the techniques used to
reveal extranodal pacemakers in the patients compared with those used in the dogs. In the animals, stimulation of both sympathetic and parasympathetic nerves and infusions of adrenergic and cholinergic agonists and antagonists were used to change the rate and shift the pacemaker site. \textsuperscript{25–30} The canine studies were designed to reveal the entire spatial-functional range of atrial pacemakers. By contrast, in these studies in patients, only overdrive stimulation was used and the escape of extranodal pacemaker sites at the shortest cycle lengths tended to obscure the more inferior pacemakers and those with slower rates.

The existence and particular operation of an atrial pacemaker complex in the human necessitates an attempt to explain its mechanism and to answer certain related questions: (1) Could some phenomenon other than an atrial pacemaker complex account for the findings? (2) Assuming the existence of an atrial pacemaker complex, what accounts for MCO at certain times, UFO at others, and the different functional (rate) ranges observed in the previously controlled animal studies? (3) What mechanisms determine the coordinated response of so many widely separated and independent pacemaker sites?

An alternative explanation for the multiple widely distributed islands of early activity is the existence of some form of complex conduction resulting in multiple sites of epicardial breakthrough of impulses that originated from a single remote pacemaker located intramurally. Arguing against such a mechanism is the thin, two-dimensional atrial geometry coexisting with the wide gaps between the separate sites of earliest activation. This mechanism would require a specialized form of conduction with multiply insulated tracts capable of propagation velocities of up to 3 m/sec. There are sufficient data to rule out this possibility. \textsuperscript{46–48}

Some degree of discontinuous conduction is inherent where endocardial strands of pectinate muscle span several millimeters. However, this mechanism is unlikely at distances between two origin points of 1 cm or greater.

The most convincing evidence for a distributed system of pacemakers and against complex conduction is the concomitant change in origin point and rate of the pacemaker in the canine studies, which implies an exchange of dominance among competing pacemakers. The association between site and function can be attributed to a single event, whereas if complex conduction were the principal mechanism, three separate events would have to occur simultaneously: (1) a change in rate, (2) a change in conduction applied differentially over multiple exit pathways such that unidirectional block or delay occurred selectively in one path and not in another, and (3) conduction of multiple impulses from a single remote pacemaker for long distances in concealed pathways (specialized conduction). The events documented in figure 6 provide further evidence that a system of distributed atrial pacemakers is the explanation for the observations presented in this report. In this patient, a left atrial pacemaker interacts with an upper right atrial pacemaker in determining the pattern of atrial activation. The two sites independently dominate during sinus rhythm in figure 6, A, and with the left atrial escape in panel D of this figure. Additionally, participation of these two sites resulting in two different degrees of fusion between left and right atrial wavefronts in figure 6, B and C, are demonstrated as the pacemaker conditions shift gradually between the two extreme sites. Complex conduction could hardly be considered as an explanation for impulse origin at two such distant sites. Interaction between two widely separated pacemaker sites is the only reasonable explanation for these patterns of exchanging dominance and fusion. Note that this interaction is analogous to the interaction between the different right atrial pacemakers. A complete explanation of the findings in these patients is not within the scope of this study. However, in extensive studies in the dog, which also demonstrated a pacemaker complex, it was possible to arrive at an explanation based on correlations between rate, maps of changing pacemaker conditions, and incremental levels of adrenergic and cholinergic stimulation. This explanation assumes: (1) multiple, widely separated pacemaker zones, and (2) a receptor-based modulation of the system based on a spatially ascending incremental sensitivity to adrenergic and cholinergic inputs. In this model, multiple distributed pacemakers compete and either dominate (UFO) or share dominance (MCO) as a result of site specific sensitivity to both adrenergic and cholinergic agonists conferred by the differential characteristics of \( \beta \)- and muscarinic receptors modulating pacemaker cells at each region. This would not only result in an associated change in pacemaker site as rate reached certain limits, but the reverse side of this same mechanism would result in a coordinated (integrated) rather than chaotic participation due to the incrementally graded dose-response continuum of the dispersed pacemaker tissue.

**Clinical implications.** It is common to note changes in the P wave during exercise testing with sinus tachycardia, during rest with sinus bradycardia, during vagal stimulation, and cycle-to-cycle during sinus arrhythmia. Brody et al. \textsuperscript{34} were the first to systematically
document that normal human subjects may demonstrate multiple different P wave morphologies. They suggested that these differences could be due to change in the site of the atrial pacemaker. In previous canine studies, we demonstrated that different P wave morphologies represented different global atrial activation patterns resulting from different sites of impulse initiation. The results of these studies in patients indicate a similar correspondence, namely that each distinctively different P wave represents a different pattern of impulse initiation with predominance of a different pacemaker region. Therefore, the use of techniques such as stress testing, tilting, Valsalva maneuver, or infusions of autonomic agonists and antagonists that directly or reflexly modify heart rate incrementally might be useful in clinical protocols in which change in cycle length is correlated with change in P wave morphology as an indicator of the number and integrity of individual atrial pacemaker regions.

The present human data confirm previous canine data indicating that tall P waves in lead aVF, associated with a more inferiorly directed P axis during “sinus tachycardia,” result from the more superiorly positioned site of impulse origin at the anterior SVC-RA junction, or “Remak’s zone.” Also confirmed is that the lower amplitude P in lead aVF associated with the smaller initial peak, followed by a larger second peak and less inferiorly directed P axis, is more frequently associated with the typical sinus location of impulse origin in the posterolateral SVC-RA junction. Finally, according to this and previous studies, the lowest amplitude P in lead aVF associated with a more horizontal P axis and a rate of 60 or less is related to domination of “Fredericq’s pacemaker,” which is located in the vicinity of the junction between the intercaval band and the inferior limbus of the SVC. This is also the P wave morphology that is frequently present after β-blockade. All three P waves can be recorded during the course of an exercise test in certain subjects with a low resting heart rate.

A point relevant to the clinical determination of sinoatrial node function with use of sinoatrial node conduction time and recovery time is the variable distance and conduction time between competing pacemakers. Clinical sinoatrial node conduction time assumes stable pacemaker location and function. The present data indicate that if the pacemaker position changes from the sinoatrial node to some other site after pacing, the values for sinoatrial node conduction time and SNRT will vary as a function of this change in distance as well as differences in conduction time between the pacing-recording electrodes and the new pacemaker site. This point has also been emphasized in reports by Gomes and Winters and Yee and Strauss. Just as the premature escape of an atrioventricular junctional pacemaker eliminates the possibility of assessing SNRT, the escape of extranodal atrial pacemakers will complicate the estimation of this variable. In fact, the SNRT estimates the escape function of the APMC, which may represent an extranodal site approximately 40% of the time (table 1).

Atrial pacemaker dysfunction syndromes, with and without associated atrial tachyarrhythmias, are noted early in some patients and late in others after cardiovascular surgical procedures. These may be related to direct damage to atrial pacemaker tissue, impaired circulation to the distributed atrial pacemakers, or to partial and progressive denervation leading to autonomic neural imbalance. In view of the widespread distribution of the human atrial pacemaker tissue in the right atrium, it could be important that the surgeon avoid damage to the 7.5 × 1.5 cm zone encompassing the atrial pacemaker complex, as well as its circulatory supply.

The findings in these patients, as well as those in the previous canine studies, suggest that the terms “sinus rhythm,” “sinus tachycardia,” “sinus bradycardia,” “sinus arrhythmia,” etc. must be reconsidered if they are used to mean a focal site of electrogensis specifically associated with the histologic sinoatrial node. However, considering that the embryologic sinus precursor encompasses all of these pacemaker sites, there is no good reason to change the terminology — only its meaning. It follows that in the presence of a widely distributed system of atrial pacemakers, the term “sinus node dysfunction” is inaccurate since more than the sinoatrial node may be at fault. The problem could vary from focal sinoatrial node dysfunction with either normal or abnormal operation of other atrial pacemaker sites to widespread involvement of atrial tissue, its circulation, the cardiac nerves, and other systems affecting the entire pacemaker complex.

Review of previous data indicates that sites of increased automaticity in patients with abnormal ectopic atrial tachycardia are frequently located at sites identified with the normal extranodal atrial pacemakers. Abnormal automatic foci have been observed at the anterior SVC-RA junction by Wyndham et al., in the inferior right atrium in one of our patients, and in the left atrium in association with the left pulmonary vein. These may represent important extranodal pacemaker sites that may have either escaped cholinergic control, have acquired increased adrenergic sensitivity, or have developed entrance but not exit block.
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