Mapping the Conversion of Atrial Flutter to Atrial Fibrillation and Atrial Fibrillation to Atrial Flutter
Insights Into Mechanisms

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Abstract It is not generally believed that there is a relation between atrial flutter, thought to be due to a single reentrant circuit, and atrial fibrillation, thought to be due to simultaneously circulating multiple-reentrant wave fronts. However, there are many reasons to suggest that these rhythms are more closely related than previously thought. To test the hypothesis that the length of an area of functional block in the right atrial free wall is critical to the conversion of atrial flutter to atrial fibrillation and of atrial fibrillation to atrial flutter, we studied spontaneous and ATP-induced conversion of stable atrial flutter to sustained atrial fibrillation and spontaneous conversion of sustained atrial fibrillation to stable atrial flutter. We studied 13 episodes of the conversion of stable atrial flutter to sustained atrial fibrillation and sustained atrial fibrillation to stable atrial flutter in seven dogs with sterile pericarditis. Six episodes were spontaneous and seven were ATP related. All episodes were studied by using a multisite mapping system to record 190 unipolar electrograms (converted in the software to 95 bipolar electrograms) from the right atrial free wall along with ECG lead II. Atrial flutter induction was attempted by atrial stimulation (S1S2 or S1S2S3) or by rapid atrial pacing for 120 beats from selected sites at selected rates. For both the spontaneous and the ATP-related episodes, stable atrial flutter was defined as any episode of ≥ 5 minutes, and sustained atrial fibrillation was any episode of ≥ 1 minute. During all the episodes of stable atrial flutter, a line of functional block with a mean length of 24±4 mm was localized on the right atrial free wall. When the previously stable line of functional block decreased to a mean of 16±3 mm (P<.05), either spontaneously or after ATP administration (40 mg IV), the new line of functional block was not long enough to maintain stable atrial flutter, and conversion to atrial fibrillation resulted. This shortened line of functional block continued to change and migrate over the right atrial free wall throughout sustained atrial fibrillation. These observations were similar for both spontaneous and ATP-induced conversions. When sustained atrial fibrillation evolved to stable atrial flutter, there was reformation of a long line of functional block, long enough (≥ prior length) to create a stable reentrant circuit, which then captured the right atrial free wall and subsequently both atria. This increase in the length of the line of functional block always occurred over several beats. In the sterile pericarditis model, conversion of atrial flutter to atrial fibrillation and conversion of atrial fibrillation to atrial flutter are closely related phenomena. Changes in the length of the line of functional block in the right atrial free wall are critical for these conversions. (Circ Res. 1994;74:882-894.)

Key Words • atrial flutter • atrial fibrillation • reentry • functional block • supraventricular arrhythmias

It has long been recognized that atrial flutter can change to atrial fibrillation and that atrial fibrillation can change to atrial flutter,1 be it spontaneously or as a result of an intervention (eg, drug administration, DC cardioversion, or atrial pacing; the latter, of course, only with atrial flutter).2 How this occurs is not well understood. Moreover, an understanding of this process, ie, the conversion of atrial flutter to atrial fibrillation and of atrial fibrillation to atrial flutter, should provide important insights into understanding both these important clinical arrhythmias. Our labora-

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Materials and Methods

Spontaneous and ATP-induced conversion of atrial flutter to atrial fibrillation and spontaneous conversion of atrial fibrillation to atrial flutter were studied 3 to 4 days after the creation of sterile pericarditis3 in a total of seven adult, conditioned, heart-worm–free mongrel dogs weighing 18 to 25 kg. In all seven dogs, stable atrial flutter (lasting ≥ 5 minutes) was first induced. Episodes of the spontaneous conversion of atrial flutter to atrial fibrillation and then the spontaneous conversion of atrial fibrillation to atrial flutter were studied in four dogs (two episodes per dog in two dogs, one episode per dog in the other two dogs). Also, in all seven dogs, one
ATP-induced episode of the conversion of atrial flutter to atrial fibrillation and the subsequent spontaneous conversion of atrial fibrillation to atrial flutter were studied. A total of 13 episodes were studied. All studies were performed in accordance with guidelines specified by the Institutional Animal Care and Use Committee, the American Heart Association guidelines for research animal use, and the current Public Health Service policy on the humane care and use of laboratory animals.

**Creation of the Sterile Pericarditis Model**

The canine sterile pericarditis model was created as previously described. To introduce atrial flutter could be induced with programmed stimulation, an open-chest study was performed, as we have previously described. To induce atrial flutter, atrial stimulation (S1S2 or S1S3S2) or rapid atrial pacing was performed via the use of the previously placed epicardial atrial electrodes using a modulated pulse generator (model 5325, Medtronic, Inc, Minneapolis, Minn). When stable atrial flutter was successfully induced, it was interrupted with rapid atrial pacing. Then, each dog was anesthetized with pentobarbital (30 mg/kg IV) and mechanically ventilated using an Ohmeda anesthesia machine to deliver 100% oxygen during the experiment. Arterial pressure was continuously monitored using a pressure transducer connected to a model VR-16 Electronics-for-Medicine oscilloscopic recorder. The body temperature of each dog was maintained within the normal physiological range throughout the study by using a heating pad.

**Studies of the Open-Chest State**

On the third or fourth postoperative day, after first demonstrating in conscious nonsedated dogs that atrial flutter could be induced with programmed stimulation, an open-chest study was performed, as we have previously described. To induce atrial flutter, atrial stimulation (S1S2 or S1S3S2) or rapid atrial pacing was performed via the use of the previously placed epicardial atrial electrodes using a modulated pulse generator (model 5325, Medtronic, Inc, Minneapolis, Minn). When stable atrial flutter was successfully induced, it was interrupted with rapid atrial pacing. Then, each dog was anesthetized with pentobarbital (30 mg/kg IV) and mechanically ventilated using an Ohmeda anesthesia machine to deliver 100% oxygen during the experiment. Arterial pressure was continuously monitored using a pressure transducer connected to a model VR-16 Electronics-for-Medicine oscilloscopic recorder. The body temperature of each dog was maintained within the normal physiological range throughout the study by using a heating pad.

**Creation of Complete Heart Block**

During induced atrial flutter in our sterile pericarditis model, 2:1 atrioventricular (AV) conduction usually occurs, and occasionally even 1:1 AV conduction occurs. Therefore, temporal superimposition of ventricular activation with atrial activation can interfere with interpretation of the recorded unipolar atrial electrograms. To avoid this, we produced complete AV block by performing radiofrequency ablation of the His bundle by use of standard electrode catheter techniques before the chest was opened. Thus, an electrode catheter specially designed for delivery of radiofrequency energy (Mansfield 7F steerable Polaris catheter with a 4-mm electrode tip) was advanced through a femoral vein to the His bundle recording position. By use of an RFG-3C RF lesion generator system (Radionics Inc, Burlington, Mass), His bundle ablation was performed. Then, ventricular pacing was initiated at a rate of 80 to 100 beats per minute by using the previously placed ventricular electrodes. Ventricular pacing was performed at 60 beats per minute during the data acquisition (simultaneous multisite recording) portions of the studies to decrease still further periods of temporal superimposition of atrial and ventricular events. Ventricular pacing was performed using a modified Medtronic 5375 external ventricular-inhibited pulse generator.

**Thoracotomy and Placement of Electrode Array**

After the above procedure, the chest was opened, and the heart was exposed while using standard surgical techniques. After the heart was exposed, a previously described electrode array containing 190 unipolar electrodes (Fig 1) arranged in 95 bipolar pairs (Fig 2) was placed on the right atrial free wall and secured with a Velcro belt. The interelectrode distance of each bipolar electrode in the array was 1.5 mm, and the distance between the center of each bipolar electrode pair and its neighbor was 4.2 mm diagonally and 6 mm perpendicularly (Fig 2). These known distances between electrodes were used when measuring the length of lines of functional block and permitted the length of the line of functional block to be calculated to the nearest 4.2 mm. After placement of the electrode array, atrial flutter was induced by the above-described standard atrial stimulation techniques.

**Multisite Mapping: Data Acquisition**

After stable atrial flutter was induced, atrial electrograms from all sites and ECG lead II were recorded during spontaneous conversions of atrial flutter to atrial fibrillation and of atrial fibrillation to atrial flutter or sinus rhythm in four dogs. Then, after at least 5 minutes of another induced atrial flutter episode in these same four dogs and in three other dogs that did not manifest spontaneous conversions of atrial flutter to atrial fibrillation, a bolus of 40 mg ATP was administered.
through a peripheral vein. Atrial electrograms from all sites and ECG lead II were recorded continuously for 5 minutes, beginning with the time of the infusion through the conversion of atrial flutter to atrial fibrillation and then the spontaneous conversion of atrial fibrillation back to atrial flutter.

Data recording and processing were performed using a cardiographic mapping system designed at Case Western Reserve University.8-10 All signals were individually amplified, filtered between a bandwidth of 1 to 500 Hz, sampled at 1000 Hz, and digitized with a 12-bit analog-to-digital converter. The data were then transferred to a 68020 coprocessor with 4 megabytes of memory via optoisolators. Data collection and processing were performed with this coprocessor (Sperry IT PC host system, IBM AT compatible). A SGT PEPPER (Number Nine Computer Corp, Cambridge, Mass) graphic processor with color monitor was used to display raw and processed data. The system had all processing units (model 68020, Sperry, and SGT PEPPER) designed to operate in parallel. This parallel organization gave the mapping system "real-time" processing capability. The system was capable of storing and archiving 30 minutes of continuous data from all electrodes. Data were archived on either a floppy disk, hard disk, or tape in their raw format.

Multisite Mapping: Data Analysis

Analysis of data consisted of selecting activation times and computation of an isochronous map with a maximum resolution of 1 millisecond. Data in both their raw unipolar format and computer-processed bipolar format (obtained by subtracting raw unipolar data from a bipolar pair) were available to assist in the selection of activation times. Data were filtered in software with a low cutoff frequency (high-pass filter) of 10 Hz before analysis to avoid baseline drift of the electrograms. A 600-millisecond analysis window was chosen from within 4 seconds of stored data. A time-reference signal was selected from one of the electrode sites and was used to depict zero activation time. The electrograms recorded at each site during the time window were displayed on a graphics screen, and selection of activation time was done manually with a cursor.

The moment of activation at each site was taken as the peak of the first rapid deflection in a predominant monophasic recording or as the time of the intrinsic deflection in a predominantly biphasic recording. The activation time at sites at which multiple-component electrograms were recorded was assigned to the major deflection (highest amplitude for bipolar electrograms or fastest downstroke for unipolar electrograms). The isolation of the first deflection of the reentrant circuit, a reference site (part of the reentrant circuit, but relatively far from an area of relative slow conduction or functional block) was selected.

Because of the differences in size of the right atrium from dog to dog, anatomic landmarks (the venae cavae, the right atrial appendage, the AV groove) were identified and positioned on the grid (electrode array) by visual inspection. For each atrial beat, activation time at each site was placed on an anatomic grid representing activation at each bipolar recording site, and isochronous lines at 10-millisecond intervals were drawn manually.

Definitions

As originally described by Wells et al,12 atrial flutter was defined as a rapid atrial rhythm (rate, >240 beats per minute) characterized by a constant beat-to-beat cycle length, polarity, morphology, and amplitude of the recorded bipolar electrograms, and atrial fibrillation was defined as a rapid atrial rhythm (rate, >260 beats per minute) characterized by variability of the beat-to-beat cycle length, polarity, morphology, and/or amplitude of recorded bipolar atrial electrograms.13 To these criteria were added criteria garnered subsequently from multisite mapping data. Thus, atrial flutter was further defined as the presence of a constant, stable, and single reentrant circuit, and atrial fibrillation was further defined as the presence of an unstable reentrant circuit (ie, one changing in both location and cycle length), more than one reentrant circuit, and/or multiple activation wave fronts (wavelets).14,15

For both the spontaneous and ATP-induced studies, stable atrial flutter was considered to be any episode ≥5 minutes in duration, and sustained atrial fibrillation was defined as a rhythm lasting ≥1 minute. Only episodes of conversion of stable atrial flutter to sustained atrial fibrillation and of sustained atrial fibrillation to stable atrial flutter were studied.

An area of relatively slow conduction was delineated by crowding of isochrones, and slow conduction, per se, was defined as conduction velocity of <0.2 m/s.16 Double potentials were defined as two discrete deflections per atrial beat, with each deflection separated by an isoelectric interval.17 A line of functional block was defined as a region of block not associated with an anatomic obstacle and not present during sinus rhythm but present only during a rapid atrial rhythm.18 A line of functional block was characterized by double potentials in which each deflection of the double potential reflected activation time on either side of the block.17,23

Documented Changes in the Line of Functional Block

Determination of the length and location of the line of functional block is a critical part of the analysis of the data. The representative example shown in Fig 3 describes and illustrates this analysis. The left panel in Fig 3 shows electrograms recorded from four closely located sites (a through d) on one end of a line of functional block, depicted by thick dashed lines, during one episode of conversion of atrial flutter to atrial fibrillation. These sites were selected for illustration because they demonstrated the appearance and disappearance of double-potential electrograms, which, along with activation times at neighboring sites, demonstrate changes in the length and location of the line of functional block during the conversion of atrial flutter to atrial fibrillation. In the right panel are displayed four consecutive activation maps from one end of a line of functional block that correspond to the beats labeled with capital letters A through D in the left panel. In the electrograms recorded from site a, a double potential is present during beat A, with local activation being represented by the first deflection and activation on the other side of the block being represented by the second deflection (*).11,17,23 With the second beat (beat B), the double potential from site a disappears, although there is a notchling in the electrogram. The knowledge of both the previous history of the electrograms recorded at this site and the activation times at neighboring sites suggests that recording site a is now very close to the end of the line of functional block (activation map B).10-22 With beat C, the double potential again appears at site a, but this time, the first deflection (+) reflects activation on the other side of the line of block, and the second deflection represents local activation.11,17,23 This is again depicted in activation map C on the right. With beat D, note that a double potential is again present at recording site a, but this time, the deflection representing local activation is first, followed by activation on the other side of the line of block (+), again depicted in activation map D on the right.

Clear double potentials are also seen in electrogram d. Thus, during beat A, a double potential is clearly present, with local activation being represented by the second deflection. The clear double potential returns during beat D, again with local activation being represented by the second deflection. Also note that sites a and d are located opposite each other.
relative to the line of block in maps A and D. When double potentials are recorded at these sites during beats A and D, the local activation at each site (the large electrogram) is reflected by a small potential at the other site (*), with the small potential representing activation on the other side of block.19-22 During beat C, although a double potential is recorded at site a, site d is sufficiently far from the functional line of block so that no double potential is recorded.

Note that throughout the four beats (A through D), only single deflections were recorded at site c. This is because this site was always too far from the area of functional block. Electrograms recorded at site b are of interest, because with beats A, C, and D, there are notches in the electrogram suggestive of closely located double potentials, previously reported to occur in proximity to the end of a line of block.21,22 Note that with beat B, electrograms recorded at site b show only a single electrogram, because that site is now sufficiently distant from the line of functional block. Also, note that during beat B, the electrogram recorded at site a also shows what can be interpreted as a closely located double potential and that during this beat, this recording site appears very close to the end of the line of functional block (activation map B).

Statistics

Data are expressed as mean±SEM. Basic comparative statistics were performed with Student’s t test for paired or unpaired data when appropriate. A confidence level of 95% was considered statistically significant.

Results

Studies of Conversion of Atrial Flutter to Atrial Fibrillation and of Atrial Fibrillation to Atrial Flutter

Six episodes of spontaneous conversion of atrial flutter to atrial fibrillation and back to atrial flutter were analyzed in four dogs. The mean duration of each episode of atrial flutter was 348±16 seconds before spontaneously converting to atrial fibrillation. The atrial fibrillation that evolved then lasted a mean of 92±4 seconds before either spontaneously reverting to stable atrial flutter or spontaneously terminating with return to normal sinus rhythm.

Seven episodes of stable atrial flutter in seven dogs were converted to atrial fibrillation 32±4 seconds after the intravenous administration of 40 mg ATP. In all episodes, atrial fibrillation went back to atrial flutter after a mean of 74±3 seconds of atrial fibrillation. In two of the latter episodes, the atrial flutter then terminated, becoming normal sinus rhythm after 67 and 49 seconds, respectively. In the other five episodes, the atrial fibrillation reverted to stable atrial flutter.

Multisite Mapping Studies of the Conversion of Atrial Flutter to Atrial Fibrillation

Fig 4 shows an isochronous map of the sequence of activation of the right atrial free wall during a representative example of stable atrial flutter (cycle length, 132 milliseconds) that later evolved into atrial fibrillation after the administration of ATP. In this case, the atrial flutter had been present for 5 minutes before the intravenous administration of 40 mg ATP. Note that the reentrant excitation wave front circulates in a clockwise direction around an area of functional block, represented by thick dashed lines, in the center of the reentrant circuit. The length of the line of functional block in this case is 24 mm. There was only one line of functional block around which the atrial flutter reentrant excitation wave front circulated in this and all other atrial flutter episodes. During all the episodes of stable atrial flutter, the center of the reentrant circuit was characterized by the recording of atrial electrograms with double potentials, each potential reflecting activation on either side of the central area of apparent functional block.4,17-22 No electrode recording site other than the ones on either side of the line of block manifested double-potential electrograms. For reference purposes, the end of the line of block closer to the
right atrial appendage will be called the RAA end, and the end closer to the inferior vena cava will be called the IVC end. As evident by the crowding of isochronous lines, there is a region of relatively slow conduction in the atrial flutter reentrant circuit that anatomically corresponds to the pectinate muscle area. Note also the reference site marked with a circle, and the lowercase letters a through f, which represent electrode recording sites for Figs 5, 6, and 11.

Fig 5 shows the atrial electrograms recorded from the selected recording sites (a through f) during stable atrial flutter (Fig 4). The first change noticed in this stable atrial flutter occurred 20 seconds after ATP administration, when the cycle length shortened, as seen in Fig 6. Fig 7 shows four consecutive activation maps from the first four beats in Fig 6. Note that the reference site (circled electrode site) was always the same throughout the study. In Fig 7, panel A is the last reentrant wave front of stable atrial flutter with a 132-millisecond cycle length. There is no difference between this map and the control map before the ATP administration (Fig 4). In Fig 7, panels A through D show the activation maps during the change in cycle length from 132 milliseconds (panel A) to 128 milliseconds (panels B and C) and 126 milliseconds (panel D). The isochrone maps are similar (Fig 7A through 7D), with no change either in the activation sequence or the line of functional block.

Fig 4. Atrial activation map of a stable atrial flutter episode that converted to atrial fibrillation after ATP administration. Figs 4 through 10 relate to this episode of atrial flutter. This and all subsequent activation maps can be described as follows: isochronous lines are drawn at 10-millisecond intervals; the circle indicates the location of the electrode pair used as the reference site for Figs 5, 6, 8, and 11; the lowercase letters a through f represent electrogram recording sites shown in Figs 5 and 6; and arrows indicate the direction of the activation wave front. CL indicates cycle length. All numbers are in milliseconds.

Fig 5. ECG lead II recorded simultaneously with electrograms from the selected electrode sites around the atrial flutter reentrant circuit shown in Fig 4. Activation times are in milliseconds. Arrows show the relative activation sequence, and thick dashed lines connect bottom and top electrograms to indicate the completion of the reentrant circuit. During stable atrial flutter, the beat-to-beat cycle length (132 milliseconds) was constant at all recording sites. Also note that some electrograms show alternans. S indicates ventricular stimulus artifact; Ref, reference electrogram.

Fig 6. ECG lead II recorded simultaneously with electrograms from same electrode sites shown in Fig 4, 20 seconds after ATP administration. Note the changes in cycle length, denoted in the reference electrograms (Ref). Note again that some electrograms show alternans. Activation maps from this sequence of activation are shown in Fig 7. S indicates ventricular stimulus artifact.

Fig 7. Four consecutive activation maps (as described in Fig 4 legend) beginning with the last stable atrial flutter cycle (map A). Note that map A is nearly identical to that of stable atrial flutter shown in Fig 4. Map B shows the activation map for the first cycle change. Note that the shortening of cycle length (CL) is associated with a disappearance of the area of relative slow conduction in the pectinate muscle region. Map C shows the next beat, which is similar to map B, and the CL is the same as well. Map D, the fourth consecutive beat shows a new 2-millisecond decrease in CL with respect to maps B and C, but there is no real difference in the activation sequence.
However, the narrow area of relatively slow conduction in the pectinate muscle region present during the control atrial flutter (Fig 4 and Fig 7A) is no longer present (Fig 7B through 7D), and a more even spatial distribution of isochrones is now seen in the whole pectinate muscle area. In fact, no more areas of relatively slow conduction in a reentrant circuit were present from this point through the clear conversion to atrial fibrillation, and almost all subsequent changes in the cycle length of the rhythm depended on changes in the length and position of the line of functional block.

Two seconds later (22 seconds after ATP administration), cycle length oscillations from 124 to 114 milliseconds appear (Figs 8 and 9). Interestingly, these cycle length oscillations do not lead to termination of the atrial flutter, as we have previously noted may occur, but rather, a smaller reentrant circuit with a cycle length of 114 milliseconds developed and became stable for 12 seconds (ie, for ≈120 beats, the last three of which are shown in Fig 10A through 10C).

Fig 8 illustrates in more detail this new shortening of the line of functional block. The left panel shows electrograms recorded simultaneously from selected sites from within the area of the square in panels D and E of Fig 9 and from the reference site along with ECG lead II during beats A through F shown in Fig 8. The right panels are an enlargement of the activation maps of the IVC end of the line of functional block shown in panels D and E of Fig 9. They also show the location of recording sites a through d. For beats A, B, C, D, and F, electrograms recorded from sites a and b show the presence of double potentials, indicating that these sites are located on one side of a line of functional block. Note also that electrograms from site c, located at the pivot point at the end of the line of functional block, show a fractionated potential. The electrograms at site d show neither double potentials nor fractionation, as this site is not in the area of slow conduction. Note also in Fig 9 that for beats A, B, C, D, and F, there is no change in the extent of the IVC end of the line of functional block. However, for beat E in Fig 8, note that there is no double potential at site b and no fractionated potential at site c and that site a shows fractionation of the major deflection of the double potential. This is because with a shortening of the IVC end of the line of functional block described in Fig 9E, site b no longer is on one side of the line of functional block (Fig 8, beat E activation map), site c is now farther away from the immediate pivot point and the area of slow conduction (Fig 8, beat E activation map), and site a is very close to the end of the line of functional block.

Fig 9 shows activation maps of the six consecutive cycles included in Fig 8. In Fig 9, panel A shows a reentrant circuit of 124 milliseconds associated with a shortening in the line of functional block (IVC end) when compared with the control atrial flutter (Fig 4 and Fig 7A). There is no further noticeable difference in the line of functional block (Fig 9A through 9D) even though there are cycle length oscillations (124 to 118 to 122 to 120 milliseconds). The fact that the cycle length...
oscillations were only between 2 and 6 milliseconds per beat may explain the lack of noticeable change in the line of functional block. A higher resolution electrode array might have been able to detect such a change if present. In Fig 9E, associated with a cycle length change to 114 milliseconds, there is a new shortening of the line of functional block (IVC end) that allows the circulating wave front to turn earlier at the pivot point (IVC end), so that the circulating wave front activates the reference site (circled) at 114 milliseconds.

Interestingly, in Fig 9, panel F shows a cycle length prolongation to 122 milliseconds and reformation to the previously longer line of block. It is clear from these maps that when changes in the length of the line of functional block occur, they precede the cycle length oscillations. However, the converse was not always true. For instance, some initial changes in cycle length were explained by the disappearance of an area of relatively slow conduction without changes in the length of the line of block. Finally, some cycle-length oscillatory changes (eg, in Fig 10C and 10D) did not have an obvious explanation. This is most easily appreciated by use of our reference site, since for every isochrone map, the head of the circulating wave front of a reentrant cycle starts at the reference site, travels clockwise around the central line of block, and then activates the reference site again. These changes in cycle length were not associated with changes in the time of conduction through an area of slow conduction. These sorts of changes were observed in both spontaneous and ATP-induced conversions of atrial flutter to atrial fibrillation and, in this representative example, were observed for a period of 35 seconds after the administration of the ATP.

In Fig 10, panels A through R show the sequence of activation maps 35 seconds after the administration of ATP. They show 18 consecutive beats beginning with the last three stable reentrant circuits with 114-millisecond cycle length through the development of classically described atrial fibrillation, as seen in the atrial electrograms in Fig 11. In Fig 10, panels A through C show the same reentrant circuit that had been present during the period of stable atrial flutter, but now with a cycle length of 114 milliseconds (it started at 132 milliseconds during stable atrial flutter; Fig 4). The decrease in cycle length was associated with a decrease in the length of the line of functional block from 24 to 16 mm. In Fig 10, panel D shows a decrease in cycle length of 8 millisecond.
onds, but no change was observed in either the line of functional block or the activation sequence. In Fig 10, panels E and F, which have virtually the same cycle length (116 and 114 milliseconds), demonstrate a change in the line of functional block, with the RAA end shifting downward. The length of the line did not change, and the activation times around the circuit remained similar, which explains the absence of any cycle-length changes. However, with the next beat (Fig 10G), an 18-millisecond decrease in cycle length (to 96 milliseconds) was present, and it is clear from the activation sequence that this decrease was again due to a shortening of the line of functional block (RAA end). With the next beats (Fig 10H through 10I), the cycle length was prolonged by 18 and 20 milliseconds, and again, the only change of consequence seen was an increase in the line of functional block to a length similar to that in Fig 10E. Changes in the length and location of the central area of block continued through the next several beats associated with changes in cycle length (Fig 10J through 10M) until a more disorganized pattern of activation evolved (Fig 10N through 10R). This was associated with the recording of atrial electrograms classic for those of atrial fibrillation (Fig 11) and with activation sequences typically found in our newly described sterile pericarditis model of atrial fibrillation. In Fig 10, panel J shows a shift and decrease in the line of functional block toward the IVC end, and the associated cycle length of 78 milliseconds was the shortest cycle length recorded during this conversion.

In Fig 10, panel K demonstrates how an increase in cycle length of 30 milliseconds (from 78 to 108 milliseconds) results from prolongation of the line of functional block in the center of the right atrial free wall. Panel L shows the activation sequence associated with the longest cycle length recorded (132 milliseconds) during this period. It was associated with the longest line of functional block (24 mm) seen during this period. Note that this length was similar to that during the period of stable atrial flutter (cycle length, 132 milliseconds) before ATP administration. However, the next beat (panel M) shows a shortening in the cycle length as a result of shortening and displacement of the line of functional block toward the inferior vena cava.

In Fig 10, panels N through R show how parts of the right atrial free wall become activated from wave fronts not part of a single reentrant circuit on the right atrial free wall. Also, panel N shows two lines of functional block, one relatively inferior, which is the center of a reentrant circuit with a cycle length of 86 milliseconds (our reference site is within this reentrant circuit), and the other relatively superior, which includes the superior vena cava as part of the line of block (a combined functional and anatomic line of block). This latter area of block may be the center of another reentrant circuit in which the reentrant wave front goes around the superior vena cava and returns to the right atrium, colliding with the other reentrant wave front (see arrows). However, because the latter potential circuit is not visualized completely, this interpretation is in part speculative. Panel O shows an area not activated (striped) within the 96 milliseconds of analysis (determined by the cycle length at our reference site). This area is fully activated in panel P, which also shows two lines of functional block but only one reentrant circuit (see arrows). Finally, panels Q and R show pseudosinus activation of the right atrial free wall, which is often seen during atrial fibrillation in our canine sterile pericarditis atrial fibrillation model. Interestingly, in panel R, there is reformation of a line of block that becomes the center of a small reentrant circuit for the next beat (not shown).

**Summary of Events During the Conversion of Atrial Flutter to Atrial Fibrillation**

During stable atrial flutter, a constant line of functional block with a mean length of 24 mm was localized on the right atrial free wall. During the conversion of atrial flutter to atrial fibrillation (Fig 12), a regular and fairly constant sequence of events was present. First, there was an acceleration of the atrial flutter rate (decrease in cycle length) due to decrease and disappearance of the area(s) of relatively slow conduction present during the stable atrial flutter. Of interest, similar observations were also noted by Pagé et al, who used vagal stimulation during atrial flutter in the canine pericarditis model. They demonstrated a slight reduction in the atrial flutter cycle length for one to
eight beats, followed by conversion to frank atrial fibrillation. However, Pagé et al did not study these phenomena any further. Second, no area(s) of relatively slow conduction reappeared. Third, the atrial rhythm that was first present after the area(s) of slow conduction disappeared resembled atrial flutter in that the activation sequence was similar to that during the stable atrial flutter, and the recorded atrial electrograms showed constant beat-to-beat morphology, amplitude, and polarity. However, the beat-to-beat cycle length varied considerably, which is atypical of stable atrial flutter. In the 13 episodes analyzed, the occurrence of beat-to-beat cycle length oscillations associated with an activation sequence similar to that of stable atrial flutter took a mean of $14 \pm 2$ seconds before a more unstable activation sequence developed. Fourth, after the latter phase, changes both in the location and the length of the line of block played a major role in the conversion. In particular, shortening of the length of the line of block (from a mean of 24±4 milliseconds to a mean of 16±3 milliseconds) resulted in the development of frank atrial fibrillation characterized by a reentrant circuit with a very short cycle length. The latter, often <100 milliseconds, acted to drive the atria very rapidly, in effect generating the atrial fibrillation. This atrial fibrillation was associated with one or two unstable right atrial free wall reentrant circuits of very short cycle lengths, which changed location and shape, disappeared, and reformed, producing atrial fibrillation. These observations were similar for both spontaneous and ATP-induced conversions. This rapid rate also necessarily exacerbated differences in refractoriness, which in turn very likely enhanced the maintenance of atrial fibrillation.

**Multisite Mapping Studies of the Conversion of Atrial Fibrillation to Atrial Flutter**

Fig 13 shows an isochronous map of the sequence of activation in the right atrial free wall during a representative example of stable atrial flutter (cycle length, 136 milliseconds; length of line of functional block, 23 mm) that spontaneously converted into atrial fibrillation after the same mechanism described above for ATP-induced conversion of atrial flutter to atrial fibrillation. In this example, after 78 seconds of the atrial fibrillation, it converted spontaneously back to atrial flutter. During the episode of sustained atrial fibrillation, and as seen during all episodes of sustained atrial fibrillation, there was no constant line of functional block in the right atrial free wall, and two or more lines of block could be present in the right atrial free wall at any given time. Fig 14 shows the electrograms demonstrating the spontaneous conversion of atrial fibrillation back to atrial flutter. In Fig 15, panels A through F illustrate six consecutive activation maps, representing the last four atrial activation sequences during atrial fibrillation and the first two activation sequences following the spontaneous conversion to atrial flutter shown in Fig 14.

In Fig 15, panel A shows a relatively simple sequence of activation for most of the right atrial free wall. It is clear that there is an absence of a complete reentrant circuit in the right atrial free wall. Note also that there is only a short line of functional block that goes toward the superior vena cava. Panel B shows that during the next activation sequence, the line of functional block enlarges (it is not possible to provide an accurate measurement, since it goes to and probably includes the superior vena cava, but within the area covered by the electrode array, it is 17 mm in length), and the activation wave front goes around it, as shown by the arrows. Another line of functional block, most likely produced by refractoriness, is present inferiorly in the right atrial free wall. This line of block prevents the wave front coming from the direction of the right atrial appendage to activate the lower portion of the right atrial free wall, which in turn permits a wave front coming from underneath the inferior vena cava to activate the latter region.

The next beat (Fig 15C) shows that the line of functional block has both lengthened (now 21 mm long) and moved, both of which result in the reappearance of a reentrant circuit (cycle length, 120 milliseconds) in the right atrial free wall. Nevertheless, the area of the right atrial free wall close to the inferior vena cava is still activated by a different wave front coming from the intercaval region. With the next beat (Fig 15D), the line of functional block undergoes more changes. Its RAA end extends superiorly, its IVC end extends inferiorly, and its center “ruptures,” the latter permitting the clockwise reentrant activation wave front to pivot “sooner” through that area. This then results in a daughter wave that activates the right atrial appendage in an inferior-to-superior direction, which in turn prevents any wave front from activating the right atrial free wall coming from the right atrial appendage (see Fig 15A and 15B). The clockwise reentrant wave front (cycle length, 90 milliseconds) pivots around the inferior portion of the line of block, but this wave front still does not activate the lower portion of the right atrial free wall, again probably because of refractoriness. Comparing the activation times of the latter area in Fig 15C and 15D, there is only a difference of 5 to 16 milliseconds from the time that area was activated in panel C by a wave front coming from the intercaval region and the time the clockwise reentrant activation wave front arrives in panel D. Therefore, it seems safe to assume that that area is not activated by the circulating reentrant wave front because it is in its effective refractory period from the activation shown in Fig 15C. Also, and very important, this lower area of the right atrial free wall (striped area) is not activated during the 90 milliseconds of the activation map in Fig 15D.

In Fig 15, panels E and F show a single reentrant circuit in the right atrial free wall with a sequence of
activation and length of the line of functional block (23 mm) similar to that of the original atrial flutter (Fig 13). Note, however, that the cycle length (102 milliseconds) is much shorter than that of the original atrial flutter (136 milliseconds). This is due to the absence of an area of relatively slow conduction at the inferior pivot point (IVC end). Note also that the inferior right atrial free wall that was not activated in Fig 15D now is activated by the circulating reentrant wave front. As in the example of ATP-induced conversion of atrial flutter to atrial fibrillation, the atrial flutter cycle length immediately before or immediately after the atrial fibrillation was much shorter than the cycle length of the initially induced stable atrial flutter. Then, over the next 5 seconds, the atrial flutter cycle length was prolonged to 136 milliseconds. The increase in cycle length was due to the reappearance of the area of relative slow conduction at the inferior pivot point (IVC end) of the reentrant circuit, so that the activation sequence was virtually identical to that of the originally stable atrial flutter.

Summary of Events During the Conversion of Atrial Fibrillation to Atrial Flutter

During all the conversions of atrial fibrillation to atrial flutter (Fig 16), a regular and fairly constant sequence of events was present. First, during atrial fibrillation, the typical activation patterns described above were present. These included many changes involving functional lines of block (their appearance, disappearance, reappearance, and changes in length). These changes ultimately led to the reformation of a long line of functional block in the right atrial free wall (greater than or equal to the prior length during the original atrial flutter). This, in turn, permitted development of a reentrant circuit that stabilized at a cycle length that then was able to capture the atria. The latter rhythm again fulfilled the criteria for atrial flutter. The cycle length of the atrial flutter was always initially relatively short but was prolonged to the original atrial flutter cycle length when the area(s) of relatively slow conduction reappeared in the reentrant circuit.

Discussion

It is now widely accepted that atrial fibrillation and atrial flutter are reentrant arrhythmias. However, their underlying reentrant mechanisms are thought to be quite different. Atrial flutter is thought to be due to ordered reentry in which a single stable reentrant circuit, almost always located in the right atrium, generates the rhythm that drives the atria. Atrial fibrillation, on the other hand, is thought to be due to random reentry in which multiple reentrant wavelets of the leading circle type continuously circulate in directions determined by local excitability and refractoriness, such that the reentrant circuits are continuously changing. Thus, it has not generally been thought that these arrhythmias are related in significant ways.

The present study, however, indicates that a considerable interrelation between these two rhythms does
exist. The analysis of the spontaneous and ATP-induced conversions between these two rhythms clearly demonstrates an interaction.

The two important factors that seem to make the difference between which rhythm is present, first (and probably foremost), the presence, length, and location of a line of functional block in the right atrial free wall and, second, the presence or absence of an area or areas of slow conduction in the reentrant circuit that circulate around the line of functional block. The presence of a long enough line of functional block in the right atrium, together with the presence of an area(s) of slow conduction, results in a stable reentrant circuit that produces stable atrial flutter. However, when the line(s) of functional block is not sufficiently long, the cycle length of the reentrant circuit shortens, and the reentrant circuit becomes unstable. The very short cycle lengths produce conditions in which wave fronts encounter areas of variously excitable to excitable tissues. This, in time, results in the generation of one or more unstable wave fronts that continue to encounter areas of refractory tissue. These wave fronts, however, permit the reformation of functional lines of block. Thus, lines of functional block form and reform in the right atrial free wall, and when one forms in the right place and is of long enough, stable atrial flutter will redevelop from the atrial fibrillation. But critical to the stability of atrial flutter is the presence of one or more areas of slow (or relatively slow) conduction. Without the latter, or as demonstrated in the present study, with the loss of the latter, the necessarily shorter cycle length of the circulating wave front results in a greater degree of head-tail interaction, which in turn appears inherently less stable or overly unstable, so that stable atrial flutter will not be possible. Critical to this, of course, is the fact that the lines of block and area(s) of slow conduction are functionally determined. This newly formed reentrant circuit will have a shorter cycle length because of the absence of the area(s) of slow conduction. The reformation of those areas will further stabilize the reentrant circuit, and a cycle length similar to or the same as the initial cycle length will reappear.

Relation to Previous Studies

There is considerable indirect support for this thesis from previously published studies. Thus, we have previously shown that induced atrial flutter in the sterile pericarditis model does not start de novo (immediately) after programmed stimulation. Rather, it first goes through a brief transitional rhythm that resembles atrial fibrillation. During the latter transitional rhythm, a long line of functional block must first form before stable atrial flutter develops. Recently Pagé et al demonstrated, in studies in the canine pericarditis model, that an induced unstable rapid atrial rhythm (probably atrial fibrillation) converted to stable atrial flutter only after the administration of procainamide, which changed electrophysiological properties such that a larger area of functional block developed in the right atrial free wall.

That atrial fibrillation may be generated by a focus (in this case, a small reentrant focus) with a very short cycle length has long been postulated. Our idea is that small unstable reentrant circuits with very short cycle lengths form, change shape and location, disappear, and reform. The cycle lengths of these reentrant circuits are so short that they generate the conduction abnormalities required to sustain atrial fibrillation. Recently, direct evidence that a single reentrant circuit with a very short cycle length (a focus) can generate and sustain atrial fibrillation has been demonstrated in an in vitro canine right atrial preparation. Also Jalife’s group, using voltage-sensitive dye studies in a right atrial preparation, has shown that rotors (reentrant circuits) with short cycle lengths can move across the tissue and then stabilize. Extrapolating from the latter observations, one could suggest that such changes in the behavior of the rotors are consistent with the rhythm changing from atrial fibrillation to atrial flutter.

Furthermore, the clinical recognition that atrial fibrillation and atrial flutter may convert from one to the other has also long been recognized. Garrey summarized the earliest such observations. More recent observations using contemporary technology include the onset of atrial flutter via a transitional rhythm thought to be atrial fibrillation in patients whose rhythms were monitored by use of ECG leads and atrial electrograms after open heart surgery or whose rhythms were induced in the electrophysiology laboratory.

Observations on Atrial Fibrillation

It is of interest that the role of functional lines of block in the atrial activation sequence we described during atrial fibrillation was anticipated decades ago by Garrey and by Lewis. Thus, as summarized by Garrey, Lewis suggested that there were similarities between atrial flutter and atrial fibrillation in that Lewis believed that in atrial fibrillation as in atrial flutter . . . there is a simple, but irregular “mother wave” circulating continuously in a sinuous path around an ill-defined ring throwing off into the outlying muscle, with every cycle, a number of centrifugal waves which cause and perpetuate its flickering fibrillation.

Our observations of the sequence of activation in the right atrial free wall during atrial fibrillation are certainly consistent with that old hypothesis. In addition, Garrey hypothesized that impulses can spread in any and all directions, their progress being limited only by the preexistence or development of localized blocks within the tissue mass. Such blocks divert the impulses into other and more circuitous paths, and the area so blocked off can participate in conduction only when an impulse which has passed the other parts of the [tissue] approaches it from another direction; this area thus in turn becomes a center from which the progress of conduction is continued, to be in turn diverted by other blocks. The existence of such blocks, and especially of blocks of transitory character and shifting location, has been noted in experiments . . . These conditions make possible the propagation of the contraction wave in a series of ring-like circuits of shifting location and multiple complexity. It is in these circus contractions, determined by the presence of blocks, that we see the essential phenomena of fibrillation.

The latter description was of ventricular fibrillation but appears in Garrey’s classic review article on auricular fibrillation and is remarkably consistent with some of the observations finally demonstrated by our multisite
mapping recordings. It is also consistent with the more recent observations of Gerstenfeld et al., who demonstrated indirectly that atrial fibrillation in humans is not entirely random and that activation wave fronts follow paths of previous excitation, describing this as linking of atrial excitation. The latter group also related the nonrandom activation patterns in atrial fibrillation to the anatomy of the atria and to changes in refactoriness that occur from previous activation.

Unanswered Questions

Many questions remain regarding the observations made. First, what starts the initial events in the transition from stable atrial flutter to atrial fibrillation is not clear. The fact that administration of ATP is known to shorten atrial refractoriness perhaps indicates that these changes are due to changes in refactoriness, but this was not tested in the present study. However, the fact that atrial fibrillation can be induced by shortening atrial refractoriness with acetylcholine either directly administered or indirectly administered through vagal stimulation has been demonstrated extensively by many investigators. On the other hand, of some interest is the recognition that type IC antiarrhythmic agents, when used to suppress recurrent atrial fibrillation in patients, sometimes “convert” subsequent episodes to atrial flutter; ie, a patient who previously presented with atrial fibrillation in the absence of drug therapy now may present with sustained stable atrial flutter, having been treated with a type IC antiarrhythmic agent to suppress episodes of atrial fibrillation. Type IC antiarrhythmic agents are thought to have little, if any, effect on refactoriness, but to the extent that they do, they minimally prolong it. Thus, what role the changes in refactoriness play in the events described in the present study requires further investigation.

Another question that is unanswered is the likely importance of the role of anisotropy in the events described. As is now well appreciated, the right atrium, and especially the anatomy of the right atrial free wall, is such that its anisotropic properties alone surely play an important role in atrial reentrant arrhythmias of all sorts, including both atrial fibrillation and atrial flutter. However, further studies are necessary to explore the role or roles of anisotropy in the events described.

In sum, the present study is consistent with several old ideas and previous observations and clearly demonstrates that atrial flutter and atrial fibrillation are not two completely different arrhythmias. Rather, they are arrhythmias that share some basic mechanisms that may explain, at least in part, the frequent occurrence of atrial flutter and atrial fibrillation in the same patient. Clearly, there is much more to be learned about these relations, but the present data provide important new insights.

References


Mapping the conversion of atrial flutter to atrial fibrillation and atrial fibrillation to atrial flutter. Insights into mechanisms.

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