Intra-atrial reentry as a mechanism for atrial flutter induced by acetylcholine and rapid pacing in the dog

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ABSTRACT In the isolated blood-perfused canine heart we produced episodes of rapid atrial flutter by continuous infusion of acetylcholine and rapid pacing. The spread of excitation during atrial flutter was mapped with the aid of two endocavitary mapping electrodes containing 960 leads and recording from 192 different sites simultaneously. The flutter maps clearly showed that intra-atrial reentry was the mechanism responsible for the arrhythmia. However, the localization and size of the intra-atrial circuits differed from case to case even in the same heart. The orifices of the venae cavae or the atrioventricular ring did not serve as a central anatomic obstacle for circus movement. We also failed to identify a special role of the internodal pathways in the formation of the loop. Instead, the intra-atrial circuits could be found everywhere, provided sufficient atrial mass was available to accommodate the circuit. The diameter of the circuits varied between 1.5 and 3 cm at a cycle length between 65 and 155 msec. The average conduction velocity of the circulating impulse varied between 60 and 80 cm/sec. Spontaneous termination of atrial flutter frequently occurred and was based on local conduction block in a narrow part of the circuit. Another interesting aspect of these studies is the finding that during continuous circus movement of the impulse, the amount of myocardium that is activated may vary considerably. This marked periodicity in excited tissue mass during atrial flutter could adequately explain the continuously undulating baseline or typical sawtoothlike F waves as seen in the surface electrocardiogram during atrial flutter.


THE EXACT MECHANISMS underlying atrial flutter in human beings are still unknown. Detailed clinical studies with intracavitary and intravesophageal leads and programmed electrical stimulation have not resulted in the identification of a single mechanism of human atrial flutter. The results of some studies were explained by assuming the presence of an ectopic focus of abnormal impulse formation,1-5 whereas other investigations point to a circus movement involving a large part of the atria.3, 6-11 Extensive epicardial mapping of the atria in patients with atrial flutter who are subjected to cardiac surgery could be an excellent and direct way to evaluate this condition. However, such studies have been scarce and do not yet allow general conclusions.12

In animal experiments various preparations of atrial flutter have been developed.13-16 In one, flutter is induced by topical application of aconitine on the exposed atrial surface.13 Another preparation is based on crushing the intercaval auricular bridge, thus converting the two orifices of the caval veins into a single but larger obstacle.14 In more recently developed preparations atrial flutter is produced by surgically induced right atrial enlargement15 or sterile pericarditis.16 Although the exact mechanisms underlying atrial flutter are not completely clarified by these techniques, the prevailing opinion is that aconitine-induced flutter is caused by a single rapidly firing ectopic focus,13 whereas the “obstacle flutter” is caused by continuous circular propagation of the impulse around the effective perimeter of an obstacle. In the present article we describe a third possible mechanism for atrial flutter, which is based on intra-atrial reentry without the involvement of a naturally present obstacle like the orifices of the venae cavae or the atrioventricular ring. It is suggested that the presence of such intramyocardial
circuits may be responsible for the rapid type of atrial flutter as found after cardiac surgery or during episodes of vagal hypertonia.\textsuperscript{17, 18} Flutter associated with atrial enlargement or pericarditis may also be based on this mechanism.\textsuperscript{15, 16}

Methods

Six mongrel dogs of both sexes weighing between 23 and 32 kg were studied. The dogs were premedicated with Hypnorm (10 mg fluanisone with 0.2 mg/kg fentanyl base), anesthetized with sodium pentobarbital (10 to 15 mg/body weight), and ventilated with a gas mixture of nitrous oxide and oxygen (2:1). The chest was opened by a midsternal incision and a pericardial cradle was made to support the heart. A special cannula (diameter 5 mm) that could be easily connected to the Langendorff perfusion column was inserted in the brachiocephalic artery. After heparinization (1 mg) the dog was exsanguinated, and the blood was collected from a cannula inserted in the superior vena cava. Two minutes after the collection of blood had started, the heart was rapidly excised. In the meantime the perfusion system was filled with the freshly collected blood and the heart was connected to the perfusion column. Perfusion pressure was measured 5 cm above the aortic valves with a Statham pressure transducer and was maintained between 50 and 60 mm Hg. The blood (total volume of about 1.01) was recirculated and oxygenated with an infant Polstan oxygenator. Temperature was kept at 37° ± 0.5°C. Acetylcholine could be added to the perfusate through a long needle whose tip extended into the aortic cannula. For continuous infusion of acetylcholine a roller pump was used with a flow between 0 and 10 ml/min.

Intracavitary “egg” electrodes. For detailed mapping of atrial excitation during arrhythmias in isolated canine hearts, we designed special, egg-shaped, multiple-recording electrodes (figure 1). The shape and size of these electrodes is such that they fit perfectly into the atria of a dog of about 25 kg. The “eggs” are solid and are made in a latex mold from a polymeric resin. Each electrode contains 480 recording wires (Teflon-coated silver wires, diameter 0.3 mm) equally distributed on the surface of the electrode, resulting in an average interelectrode distance of 3 mm. Because we did not want to disturb the excitation of the atria by making an incision in the atrial wall, the electrodes were inserted through an opening in the ventricles. An incision of about 3 cm in the free wall of the ventricles just below the coronary sulcus proved to be an easy way to insert the electrodes through the atrioventricular orifice into the cavity of the atria, one in the left and one in the right atrium. With this technique it is possible, without producing any damage to the atria, to record unipolar electrograms from 960 endocardial sites including the interatrial septum. A silver plate around the root of the aorta served as indifferent electrode.

The lower part of figure 1 shows the geometry of the atria as viewed from above in relation to the two inserted egg-shaped electrodes. The whole endocardial surface is covered by recording electrodes except for the very tips of the atrial appendages. The two solid intracavitary electrodes seemed to have no injurious effect on the condition of the atria as judged from coronary flow, rate and regularity of sinus rhythm, atrioventricular conduction, and atrial excitation during normal sinus rhythm. None of these variables was affected by the presence of the electrodes. It should be noted that although there are 960 endocardial recording electrodes, simultaneous recordings could be made from only 192. In case of a regular rhythm such as sinus rhythm or atrial flutter, activation maps can be constructed on the basis of all 960 electrodes by consecutive recording of five sets of 192 electrograms. However, during irregular rhythms or the occurrence of a single event such as the termination of atrial flutter, this is not possible; in these cases the activation maps are based on the recording of 192 unipolar electrograms. The 960 electrodes are distributed to 20 connectors receiving 48 wires each, with the input to the 192 preamplifiers divided into four groups of 48 channels. Typically the recording was started with 96 inputs connected to electrodes in each atrium. However, if a higher spatial resolution at a certain area seemed appropriate, the four input cables were connected to another combination of connectors covering, for instance, only the right atrium. This approach of plugging in four input cables of 48 electrodes into any of 20 connectors provided enough flexibility to select the most appropriate spatial resolution in any given case.

Mapping system. Figure 2 gives in a block diagram all the essential components of the mapping system. The left part depicts the recording system, and the right part shows how the data are played back for off-line analysis. For recording, 192 differential amplifiers with a filter setting of 2 to 400 Hz were used. The amplifiers were equipped with an autoranging facility that allows automatic setting of the amplification for each individual amplifier. This feature not only makes possible the operation of

\begin{figure}
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\includegraphics[width=\textwidth]{figure1.png}
\caption{The "egg" electrodes for total endocardial mapping of the atria. In the upper panel the electrodes are photographed from an anterior angle. The shape of the electrodes is ovoid except for the medial surfaces which are flattened to allow close apposition of both electrodes at either side of the interatrial septum. See text for details. The lower panel gives a superior view after the electrodes have been inserted in the atria. The ovoid shape fits exactly in the cavity of the atria. Only the very tips of the atrial appendages are not recorded. LAA = left atrial appendage; RAA = right atrial appendage; SVC = superior vena cava; IVC = inferior vena cava (modified from Allessie et al.\textsuperscript{19}).}
\end{figure}
as many as 192 amplifiers but also results in an optimal signal-to-noise ratio of the recorded electrograms. After amplification, the 192 signals are fed into three identical multiplexers (Kayser 1280-00) receiving 64 analogue inputs each. The electrograms were sampled with a sampling rate of 2000 samples/sec and digitized with eight-bit resolution. After pulse-code-modulation (Miller code), the outputs of the three multiplexers were recorded on three tracks of an analogue tape recorder (Ampex PR 2230) running at 60 ips. Except for the 64 analogue inputs, the multiplexers also received four separate digital inputs. These extra channels were used to mix a digital time code (resolution 1 msec) with the analogue data. By this direct coupling of an accurate time reference with the recorded electrograms, possible errors as caused by variations in speed of the tape recorder are avoided. Additional tracks of the tape were used to record a conventional slow time code (Systron Donner), one or two separate reference signals, and a voice log. The right part of figure 2 shows two different ways for reproducing the stored information. For conventional read-out the data are demultiplexed (Kayser 1280-10) and displayed on an oscilloscope (Tektronix 3103 N) or a pen recorder (Schwarzer). For computer analysis (PDP 11/04) the information is directly transferred to a direct memory access interface (DR11B) and stored on disc (RK05J). A Tektronix 4010 terminal was used for system communication and simple graphic output. A graphic processor (Ramtek 9051) was used for rapid display of the electrograms and for the generation of color maps.

Software was developed to transfer blocks of specified data from analogue tape to the disc, to search the electrograms for the intrinsic deflections, and to plot the set of activation times as isochronous maps together with the electrode configuration and geometric features of the heart. Figure 3 shows the different stages of the map generation program. First the configuration of the recording device and the positions of the recording electrodes are plotted (panel A). In this example the electrodes are plotted as viewed from above. To plot the total surface of the atria in a two-dimensional way, a virtual cut has been made in the inferior part of both atria extending from the atrioventricular orifice to the tip of the appendage. The free walls can then be unfolded and spread out. Next the local activation times as found by the computer are plotted at the sites where the related electrograms were originally recorded, with a color code indicating classes of isochronous activity (panel B). The activation times were calculated relative to a time reference chosen by the investigator. In this example, representing a sinus beat, the electrode recording the earliest atrial activity was used as time zero reference. Before the actual activation maps were reconstructed, the original electrograms were redisplayed on another terminal to trace possible errors in local activation times or to examine areas where the electrograms were difficult to interpret. After the set of activation times were edited, isochronic lines were generated either by hand or automatically, and the individual activation times were replaced by color-coded isochronic areas (panel C). Finally, several features such as the geometry of the heart, the electrode positions, and various symbols can be added to the map (panel D).

Results

Induction of atrial flutter. In the heart in situ, rapid atrial pacing frequently leads to atrial fibrillation and occasionally to longer or shorter periods of atrial flutter. However after isolation of the heart, provided that coronary perfusion is adequate and electrical stimuli of moderate strength and short duration are used, it becomes difficult if not impossible to induce atrial tachyarrhythmias by programmed electrical stimulation alone. The most plausible explanation for this remarkable decrease in vulnerability to atrial tachyarrhythmias of the isolated heart is the absence of parasympathetic activity. Continuous infusion of a low dose of acetylcholine (0.1 mg/liter) into the bloodstream just before the coronary arteries "restores" the naturally existing tendency of the atria to respond with short periods of atrial fibrillation or flutter after a period of rapid pacing. If the dose of acetylcholine is increased to 0.4 mg/liter the atria become highly susceptible to fibrillation and spontaneous conversion to sinus rhythm no longer occurs. In this study we used a combination of acetylcholine and rapid atrial
pacing to induce atrial tachyarrhythmias in the isolated canine heart. With this approach short periods of rapid pacing usually led to atrial fibrillation. In a minority of attempts shorter or longer periods of atrial flutter were induced. The cycle length of this type of flutter was relatively short, ranging between 65 and 155 msec. In general the stability of electrically induced rapid flutter was not very high, with the arrhythmias lasting from only several seconds to more than half an hour. Termination of flutter was always sudden. In some instances an immediate conversion from atrial flutter to sinus rhythm occurred, but in other cases atrial flutter degenerated into atrial fibrillation.

**Demonstration of intra-atrial reentry during rapid atrial flutter.** Figure 4 shows the excitation of the atria during an episode of flutter with a cycle length of 145 msec. For comparison, the map during normal sinus rhythm before the induction of flutter is given at the left. Both maps are based on the analysis of all 960 unipolar electrograms as recorded from the endocardial surface. During sinus rhythm there was a normal sequence of atrial activation. The impulse originating in the sinus
node excited the atrium along a long-stretched area at the lateral border of the superior vena cava, i.e., the crista terminalis. From here the right atrium was activated in less than 50 msec. Electrical activity in the left atrium was noted 15 msec after the impulse emerged from the sinus node. In this case the area of earliest endocardial breakthrough was located somewhat posteriorly in the left atrium. The left atrium was also activated in a regular manner, resulting in a total atrial conduction time during sinus rhythm of about 70 msec. No areas of conduction block or depressed conduction were noted.

During the episode of atrial flutter, which lasted for about half an hour, the excitation of the atria was completely different. First, it is evident that the source of the arrhythmia was located in the left atrium, the right atrium now being activated from the left. The light green area of first right atrial activation corresponds with the insertion of the bundle of Bachmann into the right atrium. Apart from the shift of the origin of the atrial impulse to the left atrium, the right atrium was activated quite normally, with the impulse spreading more or less radially from its point of entrance toward the atrioventricular ring. When the activation maps of the left atrium during sinus rhythm and atrial flutter are compared, marked differences in sequence of activation become apparent. During flutter the radial conduction pattern was lost and replaced by a continuous circus movement of the impulse in the free lateral wall of the left atrium. The length of this intra-atrial circuit was 10 cm. Since the impulse traveled around in 145 msec, the average conduction velocity along the circuit was about 70 cm/sec. However, conduction velocity along the circuitous pathway was not uniform. The part of the circuit located in the high left atrium (t = 0 to 50 msec) showed a higher conduction velocity than the part located in the inferior lateral wall (t = 50 to 145 msec).

In the lower part of figure 4, 17 unipolar electrograms recorded along the intra-atrial circuit have been selected from the total of 960 recording electrodes. The exact electrode positions are indicated on the map. For comparison, the same electrograms are shown during sinus rhythm. During sinus rhythm the area of the prospective circuit was activated almost synchronously, with the greatest difference in activation time being 40 msec. This is in sharp contrast to the excitation of this region during atrial flutter, when the 17 selected

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**FIGURE 3.** Four different stages in the process of the generation of color maps. First, the positions of the recording electrodes are displayed (panel A). See text for further details. For a correct interpretation of the maps, it is important to realize that the unfolded parts of the atrial appendages in reality are contiguous. Second, the measured local activation times are plotted at their electrode positions (panel B). At this stage, editing of parts of the map can be done after reexamining the electrograms. After the map has been edited satisfactorily the individual measurements are replaced by color-coded isochrones (panel C). Finally, features such as the geometry of the heart, special symbols, text, and a color bar can be added to the map (panel D).

**FIGURE 4.** Maps of total endocardial atrial activation during sinus rhythm (left) and an episode of atrial flutter (right). The maps are based on the recording of 960 unipolar endocardial electrograms resulting in a spatial resolution of the maps of 3 mm. Each color represents an isochrone of 10 msec. During sinus rhythm there is normal spread of the impulse from the sinus node to both the right and left atria. During atrial flutter the source of the rapid repetitive impulses is located in the left atrium and consists of an intra-atrial circuit located in the lateral wall. At the bottom of the figure 18 electrograms from 17 different sites in the left lateral wall are shown. The recording sites of these electrograms were identical during sinus rhythm and atrial flutter and are indicated on the flutter map. From these electrograms the continuous circulating excitation during atrial flutter can be seen. During sinus rhythm the area of the future circuit was excited almost synchronously and did not show any abnormalities in conduction or configuration of the electrograms.

**FIGURE 5.** Unipolar electrograms as recorded along the functional arc of conduction block representing the center of intra-atrial circus movement (right). The same electrograms are shown during sinus rhythm (left). One of the most prominent characteristics of the electrograms during atrial flutter is the presence of two components during each flutter cycle. The relative spacing of these double potentials depends on the position of the recording electrode on the central arc of conduction block. Close to the two poles of the arc of conduction block, where the circulating impulse is pivoting, the double potentials are close together. In the middle of the area of block the double potentials are equally spaced in time. The presence of this kind of double potential in a single unipolar electrogram indicates the close apposition of two opposite limbs of a circuit. The color key of the activation map is the same as in figure 4.

**FIGURE 6.** Atrial excitation maps of six different cases of rapid atrial flutter. Maps at top left and middle right are taken from the same heart. In all cases atrial flutter was based on intra-atrial reentry. There was marked variation in both the rate of the flutter and the localization of the circuit responsible for the arrhythmia. Top left, The circuit (cycle length 145 msec) was found in the lateral wall of the left atrium. Top right, The impulse circulated around the left atrial appendage with a revolution time of 115 msec. Middle left, The extremely rapid flutter (cycle length 65 msec) was based on a circuit in the posterior wall of the left atrium. The episodes of the other three cases of atrial flutter were caused by an intra-atrial circuit located around the right atrial appendage (middle right), in the left lateral wall (bottom left), and the posterior right atrium (bottom right). The estimated size of the circuits varied between 5 and 10 cm. Each color represents an isochrone of 10 msec.
electrodes bridged the entire flutter cycle of 145 msec. The electrograms along the flutter circuit did not exhibit any marked irregularities in configuration nor did they show multiple components or other signs of fragmentation or continuous activity. What they do show is that continuous conduction at more or less normal speed in a sustained intra-atrial circuit of several centimeters without the involvement of a large central anatomic obstacle is possible and may lead to rapid atrial flutter. It should be emphasized that with less extensive mapping techniques the identification of such a circuit can be easily missed. About half the length of the circuit the impulse is propagating in a rather narrow pathway along the inferior margin of the atrium. Moreover, because of the somewhat depressed conduction in this region, the electrograms were of lesser quality than those in other areas. If this limb of the circuit were to remain unrecognized, most probably the flutter would be erroneously attributed to a focus of rapid impulse formation in the low left atrium.

Figure 5 shows another selection of 16 electrograms recorded from the central arc of functional conduction block during the same episode of flutter. The exact recording sites are indicated on the map. Again, the electrograms recorded at the same locations during sinus rhythm are given for comparison. During sinus rhythm the electrograms did not show any sign of disturbed conduction. We also failed to find inexcitable areas that might have developed by inadequate regional coronary perfusion. In other words, there was no way to predict from the excitation during normal sinus rhythm whether or where intra-atrial conduction block would develop. During atrial flutter the electrograms recorded from the center of the circuit showed some distinctive features. One of the most characteristic properties is the presence of double complexes during each flutter cycle. The relative spacing of the two components of these double complexes depends on the position of the recording electrode on the arc of conduction block. At the two poles of the central line of block (electrodes 2 through 4 and 12 through 14) the two components of the extracellular complex were close together, dividing the flutter cycle in a short and a long subcycle. In the middle of the circuit (electrodes 7 to 10) the two components were more equally spaced in time, dividing the flutter cycle in two halves. Such widely separated double complexes in a single unipolar electrogram were found at sites where two limbs of a circuitous pathway were in close apposition. Electrodes positioned exactly on the line between two oncoming activation waves can “see” both waves passing along at either side. This sign can be regarded as indicative of functional conduction block, although it can also be expected in case of a thin scar caused by an intra-atrial incision.

The above data clearly show that an area of functional conduction block serves as a central arc around which the impulse circulates. However, in this particular case, because one end of the circuit was close to the left pulmonary veins, the possibility could not be completely excluded that the orifice of a pulmonary vein was also included in the circuit.

In figure 6 some other examples of atrial excitation during rapid atrial flutter are shown. In all cases the arrhythmia was based on continuous circus movement of the impulse in the atrial myocardium. However, the localization of the intramyocardial circuits differed from case to case even in the same heart. For example, the paroxysm of atrial flutter illustrated in figure 6, top left, was based on a circuit in the lateral wall of the left atrium. Half an hour later in the same heart another episode of flutter was induced (middle right). This time the impulse was found to circulate around the appendage of the right atrium. In the other cases the circuit was located around the left appendage (top right), the posterior left atrium (middle left), the lateral wall of the left atrium (bottom left), and the posterior right atrium (bottom right). The size of the circuits and the flutter cycle length also varied from case to case. In the six examples, the cycle length ranged between 65 and 145 msec, with the length of the underlying circuits varying between 5 and 10 cm. These differences may have been due in part to different effective acetylcholine concentrations leading to a different degree of shortening of the atrial refractory period.

**Periodic fluctuations in activated atrial mass during atrial flutter.** With regard to the possible clinical significance of the above-described type of intra-atrial reentry, it would be of interest to know what the configuration of F waves in the surface electrocardiogram would be during the different episodes of atrial flutter shown in figure 6. We did not attempt to record an artificial electrocardiogram from the isolated heart because we believed that detailed comparison of the electrocardiogram of an isolated heart with a standard electrocardiogram would be inappropriate. Instead we used the atrial activation maps to plot the variation in activation tissue mass during the cardiac cycle (figure 7). The tracings presented in this figure are generated by counting the number of recording sites activated throughout the cardiac cycle. On the ordinate the percentage of electrode sites activated during an isochronic period of 10 msec is plotted against time. Since the recording electrodes were equally spaced and
covered the entire endocardial atrial surface, the relative number of activated electrodes can be taken as the relative surface of the atria that is activated. The signal is not influenced by the direction of the propagating impulse nor is it modulated by cancellation of wave fronts traveling in opposite directions. This kind of tracing thus represents an estimate of the direct basic electromotive source for the atrial component (underlying P or F waves) in the body surface electrocardiogram. We refer to this signal as the "direct atrial electrocardiogram." The top panel of figure 7 shows such a "direct" atrial electrocardiogram during sinus rhythm, whereas in the lower panel the atrial activity during the case of flutter described in figure 4 and 5 is given. Each panel consists of three tracings. During sinus rhythm the right atrium is fully depolarized within 60 msec. Excitation of the left atrium started 15 msec later than in the right atrium and also took about 60 msec; the total excitation of both atria during normal sinus rhythm lasted less than 80 msec.

The direct atrial electrocardiogram during the episode of atrial flutter (figure 7, lower panel) shows some interesting features. First, it is obvious that in only one of the two atria was continuous electrical activity present. In the right atrium there were clear "isoelectric" periods (stippled segments) during which the right atrium was electrically silent. In the left atrium, where in this example the circuit was located, a continuous excitatory process was going on. However, despite the presence of this continuous activity in the left atrium, a striking periodicity in the amount of atrial myocardium depolarized was present during the flutter cycle. Although it is true that during flutter the impulse never completely died out (this would be incompatible with circus movement), the amount of left atrial tissue activated during a period of 10 msec varied from 10% to less than 1% of the total endocardial surface. In circus movement in a considerable part of the atria one might have anticipated that the amount of tissue activated during the cycle would be more or less constant. However, if one looks at the direct electrocardiogram of both atria (lower trace) this proved not to be the case. During half the flutter cycle the amount of tissue being excited was less than 5%. It is unlikely that the activation of such a small part of the atria becomes clearly visible in the body surface electrocardiogram. In figure 8 the direct atrial electrocardiograms are shown during the paroxysms of atrial flutter illustrated in figure 6. The periodicity in the amount of atrial myocardium depolarized during flutter is evident in most cases. It may be expected that this variation in electromotive force alone would lead to a continuous undulating baseline in the actual surface electrocardiogram.

**Termination of rapid atrial flutter.** In figures 9 and 10 two examples of termination of rapid atrial flutter are shown. Figure 9 shows the termination of the flutter illustrated in figures 4 and 5. The series of maps as shown in the upper part of figure 9 are based on simultaneous recording of 192 electrograms from the left atrium. To get the highest possible spatial resolution in the area of the intra-atrial circuit, which in this case was located in the free wall of the left atrium, all 192 amplifiers were connected to electrodes in the left atrium. Therefore only the activation of the left atrium is shown. Panels A to E visualize the sequence of activation of the left atrium during the last cycles of the flutter. Panel F shows the propagation of the first sinus beat. In the lower part of the figure, 15 local electrograms recorded around the left atrial circuit are dis-
played (see map A). In this case transition to sinus rhythm was induced by interruption of the infusion of acetylcholine after the flutter had proceeded for more than half an hour. Except for a slight prolongation in cycle length, in panel A the sequence of activation is still identical to that seen in the maps recorded during the stable phase of this episode of flutter (compare figures 4 and 5). However, just before the termination

![Diagram](http://circ.ahajournals.org/)

**FIGURE 8.** Direct atrial electrocardiograms from the six cases of atrial flutter shown in figure 6. Although the position of the intra-atrial circuits differs from case to case, in all instances there is a marked periodicity in the atrial tissue mass that is activated during the flutter cycles. This periodicity in underlying basic electromotive force, which is not caused by changes in the direction of the excitation wave, can be expected to cause — by itself — a sawtoothlike continuous undulation of the baseline in the surface electrocardiogram.

**FIGURE 9.** Transition of atrial flutter into sinus rhythm by washout of acetylcholine. At the top, activation maps of the left atrium during the last five cycles of atrial flutter are shown (A to E). F, Activation map of the first sinus beat after termination of atrial flutter. Each color represents an isochrone of 20 msec. At the bottom, 15 electrograms recorded along the left atrial circuit are displayed. The exact recording sites are indicated on panel A. The cycles illustrated in the maps are indicated on the electrograms by vertical dashed lines and are marked correspondingly (A to F). During the last flutter cycles the beat-to-beat cycle length prolongs progressively. This slowing down of the arrhythmia before its termination is caused by Wenckebach-like conduction in part of the intra-atrial circuit. When the Wenckebach sequence of progressive conduction delay is terminated by complete local conduction block, the circuit is broken and after a pause sinus rhythm resumes.
of flutter the cycle length progressively prolongs from 150 to 210 msec. From the corresponding maps (A to D) it can be seen that this slowing down of the flutter is caused by a progressive depression in conduction velocity in the postero-inferior part of the circuit. Probably as a result of the gradual prolongation of the refractory period by washout of acetylcholine, the area between electrodes 6 and 9 could only propagate the circulating impulse at progressively diminished speed. During cycle E complete conduction block occurred beyond electrode 6. Because the part of the atrium showing this Wenckebach-like conduction formed a narrow part of the circuit, the occurrence of localized intra-atrial conduction block resulted in sudden termination of the arrhythmia. The first sinus beat after cessation of flutter (panel F) shows normal excitation of the left atrium, with the sinus impulse entering the left atrium predominantly through Bachmann's bundle.

Figure 10 shows a somewhat different spontaneous termination of another episode of atrial flutter. This time the flutter was based on circus movement around the right atrial appendage (cycle length 100 msec). Again there was significant variation in width of the excitation wave along the circuit. Although the wave-front was broad passing along the superior and lateral part of the right atrium, it became rather narrow while traveling up again at the inferior and medial wall of the appendage. In this example atrial flutter was suddenly interrupted without diminishing the acetylcholine concentration and without any previous change in cycle length or activation pattern. The maps of the last two cycles show that termination was caused by sudden conduction block in the narrow part of the circuit at the medial wall of the right atrial appendage. Unlike the example shown in figure 9, in this case there was no preceding Wenckebach-like slowing in conduction in the narrow portion of the circuitous pathway. There was also no slowing of the rate of the flutter before its termination.

Discussion

The present studies show that in isolated healthy canine hearts, paroxysms of rapid atrial flutter can be induced when atrial refractoriness is shortened by administration of acetylcholine. Mapping the sequence of activation of the atria clearly demonstrated that this arrhythmia is based on intra-atrial reentry. No special anatomic defined site of preference was found. In fact, the localization of the reentrant circuits was highly variable and actually could be found everywhere, provided there was sufficient atrial mass available to accommodate the circuit. The size of the identified intra-atrial circuits was neither large nor very small, with the length of the circuitous pathway varying between 5 and 10 cm (diameter 1.5 to 3 cm). Our findings differ in this respect from those of studies in which the impulse was believed to circulate around a large natural or/artificial obstacle. 6, 7, 11, 14, 20, 22 Although the exact pathway of the impulse during this 'obstacle flutter' could not be mapped accurately because of the limited number of sites recorded in those studies, they emphasized the special role of the superior and inferior venae cavae to serve as a central anatomic obstacle large enough to create an excitable gap between the crest of the circulating impulse and its own tail of refractoriness. Boineau et al. 23 produced atrial flutter by focal suture ligation of the crista terminalis. Their maps suggest that an area of depressed conduction at the area of the tuberculum intervenosum was the pathologic substrate for atrial flutter. We also failed to find evidence for the suggestion made by Pastelin et al. 24 that the so-called specialized internodal pathways play an important role in the genesis and maintenance of circus movement flutter.

In earlier studies on experimental flutter in isolated rabbit atria we have described reentry without the involvement of an anatomic obstacle (the leading circle concept). 25-27 In the rabbit, the diameter of these functionally determined circuits varied between 0.6 and
0.8 cm. Since in this type of circus movement the length of the circuit is equal to the wavelength of the circulating impulse, there exists no gap of full excitability. The rate of such a reentrant rhythm is primarily governed by the refractory period of the tissue in which the impulse circulates. It is as fast as the highest possible rate that can be followed by all parts of the circuit. In the examples of rapid flutter described in the present canine study, large anatomic obstacles were equally not involved. Although in some of our cases it could not be excluded that the orifice of a pulmonary vein was enclosed in the circuit, the mechanism of rapid atrial flutter in the isolated canine heart was similar to the "leading circle" type of reentry described in a syncytium of rabbit myocardial cells. The larger dimensions of intramyocardial circuits in the dog compared with the rabbit must be explained by species differences in the wavelength of the cardiac impulse. In the canine atrium the refractory period is longer and the conduction velocity is faster than those in the rabbit. Since the length of the excitation wave is the product of the refractory period and the conduction velocity, this will result in a considerably longer wavelength of the impulse in the canine atrium. Because it is impossible for the impulse to circulate in a pathway shorter than its own wavelength, the minimum size of intramyocardial circuits is determined by the length of the excitation wave. This relationship may not only account for differences in size of intramyocardial circuits in different species but may also offer an explanation for the effects of some antiarrhythmic drugs. In general it can be anticipated that drugs that increase the wavelength of the impulse will be effective in preventing the occurrence of intramyocardial reentry. On the other hand, agents that shorten the wavelength (such as acetylcholine) will facilitate intra-atrial reentry, making the heart more vulnerable to rapid atrial flutter and fibrillation.

**Direct atrial electrocardiogram.** The presence of continuously undulating F waves in the electrocardiogram during atrial flutter has been thought to support the possibility of circus movement as the underlying mechanism. Besides the fact that the presence of continuous electrical activity per se is not sufficient proof for reentry, our records of a direct electrocardiogram suggest that there may even exist an isoelectric period during reentry involving a large part of the heart. The maps during atrial flutter show that during a considerable part of the flutter cycle, only a relatively small portion of the atrial mass is excited because of the existence of a narrow isthmus in the intra-atrial circuit responsible for the arrhythmia. The amount of tissue activated during circus movement can only be expected to be constant if the impulse circulates at constant speed in the central area of the atria. However, if the localization of the circuit is at the periphery, adjoining the atrioventricular border, a marked periodicity in the amount of activated atrial tissue must be present. During about half the cycle when the impulse is traveling in the inferior atrium, only myocardium that is part of the circuit itself will be activated because conduction in the direction of the atroventricular ring is not possible. Only during the other part of the cycle, when the impulse is in the superior part of the circuit, can the rest of the atria be excited. This would imply that any intra-atrial circuit in which the impulse travels in a craniocaudal and caudocranial direction would lead to a clear periodicity in electromotive force independent of the exact localization of the circuit and regardless of whether the impulse circulates in a clockwise or a counter-clockwise direction. Such periodicity was indeed present in most cases of atrial flutter in which a regional circus movement in the atria was identified (figure 8). This means that the periodicity in electromotive force alone might result in a regular and constant undulation of the baseline in the surface electrocardiogram irrespective of the cyclic changes in direction of the depolarization wave. It also means that isoelectric segments may exist in the surface electrocardiogram during circus movement flutter, reflecting the participation of a narrow isthmus of atrial muscle, most probably situated in the inferior atrium neighboring the atroventricular ring.

**Various types of atrial flutter.** Recently Wells et al. distinguished two different types of atrial flutter primarily based on differences in atrial rate. They divided 27 patients developing atrial flutter after open heart surgery into two groups. Group I (18 patients) showed classic (common) atrial flutter with an atrial rate ranging from 240 to 338 beats/min. In group II (nine patients) the atrial rates ranged from 340 to 433 beats/min. Both types of flutter were characterized by a strikingly constant beat-to-beat interval, morphology, polarity, and amplitude of the atrial electrograms. The main reason these authors separated atrial flutter into type I, with a rate slower than 340 beats/min, and type II, with a rate higher than 340 beats/min, was the observation that rapid atrial pacing from the high right atrium always influenced type I flutter, whereas it never influenced type II atrial flutter. Conversion of atrial flutter by rapid pacing and/or reset of the flutter cycle with a properly timed single stimulus strongly points to the existence of a reentry circuit with an excitable gap. Thus the slower examples of atrial flutter (type
I) should be based on circus movement including an appreciable excitable gap. On the other hand, failure to interrupt flutter by overdrive pacing suggests that the excitable gap is either very small or absent, resulting in effective shielding of the circuit from interference with oncoming activation waves. Accordingly, rapid atrial flutter (type II) seems to be based on the same kind of functionally determined intramyocardial reentry as demonstrated in the present experiments.

Different types of intra-atrial reentry. Circus movement in the atria as a cause of atrial flutter and fibrillation comprises a wide spectrum of variations. At one end is circus movement around a large anatomic obstacle. At the other end there is the possibility of a small functional intramyocardial circuit without an excitable gap, as originally identified in isolated pieces of rabbit myocardium. Between these two extreme examples of circus movement a wide variety of intermediate types of reentry of various sizes and with different excitable gaps may exist. The presence of diseased atrial tissue with abnormal electrophysiologic properties may further add to the complexity of intra-atrial circus movement in patients. When areas of depressed conduction are participating in a reentrant circuit, the rate of the resulting flutter will be slow and inhomogeneities in conduction velocity and refractory period along the circular pathway will exist. Such inhomogeneities will result in differences in width of the excitable gap along the circuit.

In figure 11 various types of intra-atrial circus movement are shown. Panel A shows the earliest model of circus movement as introduced by Mines in 1913. It is the simplest model of reentry, in which the impulse continuously encircles a large anatomic obstacle. Implicit to this model is the existence of an excitable gap (white part of the circuit) between the crest of the excitation wave and its tail of refractoriness (dotted area). The presence of such an excitable gap explains the high degree of regularity and stability of this kind of rhythm. Since the studies of Rosenblueth and Garcia Ramos there is little doubt that by the creation of a large obstacle in the atria, atrial flutter can be produced that is based on this mechanism. The problem however is that in patients suffering from atrial flutter such large anatomic obstacles have never been actually demonstrated.

In panel B circus movement around two obstacles (like the venae cavae) as popularized by Lewis is shown. A functional conduction block is assumed in the isthmus between the two obstacles. As long as the excitable gap remains shorter than the circumference of the smallest of the two obstacles, short-circuit of the circulating impulse through the interobstacle band is prevented and the flutter rate is determined by the revolution time of the impulse around both obstacles. The behavior of this type of reentry is identical to that of the model shown in panel A with one exception. As soon as the excitable gap gets larger than the perimeter of the smallest obstacle, the impulse can shortcut the circuit. This may result in either sudden termination of flutter (an event that occurred so frequently in Lewis’ experiments that it almost invariably prevented complete mapping of the excitation of the atria) or, when the impulse continues to circulate around the larger obstacles, in abrupt acceleration of the flutter. When in this case other parts of the atria cannot follow the higher rate, degeneration into atrial fibrillation may occur.

In another attempt to overcome the problem that natural obstacles in the atria do not seem to be large enough to allow for sustained circus movement, Moe...
and collaborators\textsuperscript{\textit{24}–\textit{29}} modified the early model of Mines by taking differences in conduction velocity in the atrium into account. In Moe’s model (panel C) the role of rapidly conducting muscle bundles like the internodal bands and the bundle of Bachmann is emphasized. The idea is that the internodal pathways forming closed loops may serve as preferential circuits through which flutter waves may circulate. The greater conduction velocity in these muscle bundles would abandon the necessity for a large physical obstacle. For instance, by assuming that the conduction velocity in a loop of internodal bands is twice as rapid as in normal myocardium, the effective perimeter of any natural opening present within that loop will be doubled.

In panels D and E we propose some additional variants of intra-atrial circus movement that may be responsible for common atrial flutter in human beings. They are based on a combination of a physical obstacle and an adjacent area of diseased tissue. In panel D an area of depressed conduction is assumed in the inferior atrium between an internal obstacle (like a pulmonary vein or the inferior vena cava) and the atrioventricular ring. Let us assume that the circumference of the internal obstacle is 9 cm and let the shortest possible cycle length of a sustained atrial rhythm be 140 msec at a conduction velocity of 70 cm/sec. If the obstacle is completely surrounded by healthy tissue, circus movement around the obstacle would be impossible because the impulse would complete a full cycle within 130 msec, 10 msec less than the atrial fibers need to restore their excitability. However, if one-third of the loop in the isthmus between the internal obstacle and the anulus fibrosis consists of depressed atrial tissue with a conduction velocity of 30 cm/sec, it would take the impulse 190 msec to travel around the orifice. Not only would the rate of such reentrant rhythm be within the range of common atrial flutter, it can also be expected to be stable and long lasting because now in the healthy segment of the circuit there exists an excitable gap of 50 msec.

In panel E a functional arc of conduction block extends to an internal anatomic obstacle. The revolution time in such a circular pathway may be long enough to create an excitable gap in the normal atrial myocardium. Only at the free end of the arc of conduction block is there a tight fit between the crest of the circulating depolarization wave and its tail of refractoriness. This functionally determined turning point then is the only unstable part of the circuit. During subsequent cycles the impulse may pivot at slightly different points, resulting in minor variations in size and cycle length of the circuit. However, the localization of the circuit will be fixed and the resulting flutter could last for a long period.

Another way intra-atrial reentry can be facilitated is by shortening of the wavelength of the impulse. The wavelength is defined as the distance traveled by the impulse during the time equal to the functional refractory period. When this occurs natural openings in the atria may suffice as central anatomic obstacles for stable circus movement (panel F). Conditions that shorten the excitation wave also favor circus movement without the involvement of any physical obstacle. Relatively small arcs of functional conduction block that may arise during atrial premature beats or rapid pacing then may be sufficiently large to permit rapid self-sustained reentry without the involvement of an anatomic obstacle (panel G). This mechanism generates the fastest possible atrial rhythm. If there is only one circuit present and the rest of the atria can follow the high rate in a 1:1 fashion, rapid atrial flutter will result. The episodes of acetylcholine-induced atrial flutter analyzed in the present studies were based on this type of reentry. It seems likely that rapid atrial flutter (type II) that may occur after cardiac surgery\textsuperscript{\textit{17}} is also based on this mechanism. The same type of intra-atrial reentry (around a functional arc of conduction block) may be the basic element underlying atrial fibrillation.

We do not believe that the kind of circus movement visualized in this study is responsible for the slower type of atrial flutter. Not only was the rate of the flutter in our experiments too high for common atrial flutter, but also the absence of an appreciable excitable gap excludes the possibility that such rhythm can persist for weeks, months, or even years. Evidence has accumulated to suggest that an excitable gap of about 15% to 25% of the flutter cycle exists in human atrial flutter.\textsuperscript{\textit{7, 8, 9–11}} Catheter mapping and programmed electrical stimulation during atrial flutter point to an area of slow conduction located somewhere in the inferior atrium. Puech et al.\textsuperscript{\textit{7}} noted an isthmus of slow conduction in the inferior right atrium in the vicinity of the coronary sinus. Using programmed electrical stimulation, Wellens\textsuperscript{5} observed that the time relations of atrial flutter could be influenced more often when premature stimuli were given low in the atrium than when stimuli were applied in the high right atrium. Recently Inoue et al.\textsuperscript{\textit{10}} and Disertori et al.\textsuperscript{\textit{11}} reported that the degree of reset of the flutter cycle by the application of a single premature stimulus was dependent on both the site of stimulation and the site of recording. Together with the studies of Leier et al.\textsuperscript{\textit{30}} and Cosio et al.,\textsuperscript{\textit{31}} who showed that clinical atrial flutter is associated with depressed atrial conduction, these observations lead us to believe
that common atrial flutter can best be understood by a special interplay between the anatomy of the atria and the presence of abnormal electrophysiologic properties at some strategic areas. The crucial point to be elucidated in relation to the mechanism of classic atrial flutter is the question of which electrophysiologic and/or structural abnormalities create the appropriate conditions for an excitable gap.

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