Vagally Induced Block and Delayed Conduction as a Mechanism for Circus Movement Tachycardia in Frog Atria

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Episodes of tachycardia induced by strong vagal stimulation in spontaneously beating isolated atria of frog (Rana temporaria) were studied with multielectrode mapping technique. These episodes were inducible in 19 of 39 preparations. The arrhythmia started several seconds after cessation of vagal stimulation strong enough to cause sinus arrest, without electrical stimulation of the myocardium. The arrhythmia consisted of two to 20 beats (6±4, mean±SD, n=42) with a cycle length of 100–500 msec. Recording from 32 sites with spatial resolution of 1–2 mm showed that the arrhythmia was due to intra-atrial circus movement. The estimated perimeter of the reentrant circuit ranged from 6 to 20 mm. In circuits of the minimal size, the average conduction velocity along the circuit was as low as 2–3 cm/sec. Paroxysms of the tachycardia were always preceded by vagally induced nonuniform depression of conduction, with some areas of atria being completely blocked. As the vagal influence decreased, the blocked areas recovered in an inhomogeneous manner, their unblocking being significantly (p<0.05) delayed after inhibition of tissue cholinesterase by proserine. The reentrant tachycardia was initiated when a sinus impulse arrived during certain phase of the unblocking. Unlike the well-known mechanism of reentrant excitation, which is based on inhomogeneous refractoriness and critically timed extrabeat(s), the circus movement in our model depended on vagally induced conduction block and could be launched by a single sinus impulse. (Circulation Research 1989;64:213-226)

It has been shown that some atrial tachycardias, particularly atrial flutter, can be caused by circus movement of the excitatory impulse,1–6 and cholinergic influence favors induction and perpetuation of such arrhythmias.3,7 Arrhythmogenic action of acetylcholine and its derivatives are usually interpreted as a result of nonuniform shortening of the action potential, which leads to increased probability of the circus movement.8,16

Initiation of intra-atrial circus movement is commonly considered to be connected with inhomogeneous atrial refractoriness and premature beat(s).1,9–12 However, episodes of rapid atrial tachycardia can be induced solely by intensive muscarinic stimulation in the absence of rapid pacing or extrastimulation.13–18 Studies in which two microelectrodes were used in isolated frog atria preparation19 showed that paroxysms of rapid atrial tachycardia secondary to vagal stimulation were connected with restoration of excitability in some zones of the atria blocked by the vagal nerve. It was supposed that such temporarily blocked zones could lead to circus movement, thus serving as a site of unidirectional conduction.20

The present study was designed to evaluate the proposed mechanism of reentry secondary to vagal stimulation by direct mapping of excitation sequence during vagally induced tachycardia in isolated frog atria. Data obtained showed that 1) strong vagal stimulation induces inhomogeneous slowing and block of conduction in atria; 2) during the recovery from vagal influence, a single sinus impulse could initiate circus movement by being blocked antegradely in the unexcitable zone and passing through this zone retrogradely; and 3) vagally induced slowing of conduction was an essential prerequisite for occurrence of the circus movement in a small specimen of atrial tissue (about 10×10 mm) and enabled reentrant circuits of very small lengths (6–8 mm) to occur. Thus, this report represents an example of reentrant tachycardia that is completely dependent on vagally induced depression and block of atrial conduction.

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Preparation and easily damaged by the electrodes, so it was on the epicardial surface of the atria. The 10x5 mm superior venae cavae; LVN and RVN, vagal nerves.

The remaining preparation consisting of atria, interatrial septum, sinus venosus, left atrium; RA, right atrium; SV, sinus venosus; IVC, inferior vena cava; LSVC and RSVC, left and right superior venae cavae; LVN and RVN, vagal nerves.

Materials and Methods

Preparation

Experiments were performed in November through February on frogs (Rana temporaria) weighing 100–120 g. After ligation of major vessels, the hearts were removed together with distal parts of the cardiac vagosympathetic trunci and were bathed in Ringer’s solution at ambient temperature. The sinus venosus and right atrium were opened through a cut made in the inferior vena cava. The left atrium was also opened and the ventricle was removed. The remaining preparation consisting of atria, interatrial septum, sinus venosus, and nerves was distended with ligatures on a special ring, which was regarded as conduction block. The lack of propagation, namely, isochronal lines representing subsequent positions of the excitatory wavefront. Isochronal lines were built with linear interpolation between sets of three adjacent recording sites showing activation, either automatically or manually. Decrease of conduction velocity below 2 cm/sec was regarded as conduction block. The lack of activation of electrodes under vagal influence (see

FIGURE 1. † A scheme of isolated distended atria of frog Rana temporaria. Positions of 32 recording electrodes on the epicardial surface of the atria. The 10×10 mm electrode grid is shown (see text). Another type of grid (10×10 mm) was used for atria of larger sizes and had twice as much interelectrode distance along interatrial border (vertical direction on the figure). For both grids, the electrodes covered almost all the atrial surface. LA, left atrium; RA, right atrium; SV, sinus venosus; IVC, inferior vena cava; LSVC and RSVC, left and right superior venae cavae; LVN and RVN, vagal nerves.

Multielectrode Array

An array of 32 extracellular “floating” tungsten unipolar electrodes with a tip diameter 0.18 mm, isolated except at the tip, was placed softly onto the common epicardial surface of both atria (see Figure 1). The surface of the interatrial septum was very thin and easily damaged by the electrodes, so it was excluded from mapping. Two kinds of multielectrode grids were used depending on the size of the heart. For larger hearts, we used a grid with equal interelectrode distances of 2 mm along both perpendicular directions (grid, 10×10 mm), and for smaller hearts, we used a grid in which the interelectrode distance along one of the perpendicular directions was shortened to 1 mm (grid, 10×5 mm; Figure 1). Most of the experiments were performed with a grid of 10×5 mm, which allowed more adequate distention of the atria. For both larger and smaller preparations, the electrode array covered most of the atrial surface. The distance between periphery electrodes and borders of preparation was less than 1–2 mm (Figure 1). A ring of silver wire lying on the bottom of the experimental bath served as the common ground electrode.

Considerable variability of activation waveforms on the unipolar electrograms was observed even under control conditions. This was probably due to the trabecular structure of frog atria and the different quality of contact between the electrodes and the atrial surface. For analysis, those signals with an amplitude greater than 0.2 mV and a negative deflection with maximal rate of change (−dV/dt) greater than 30 mV/sec were used. The system noise was less than 0.1 mV (usually about 0.05 mV). Those experiments in which there were more than three recording sites, which did not satisfy any of the activation criteria under control conditions, were discarded. Under vagal influence, decrease of signal amplitude correlated with depressed conduction, and failure of electrograms to reach the activation criteria was considered indicative of vagally induced block or inexcitability (for example, see Figure 3).

Mapping System

The detailed description of mapping system is given elsewhere.21 For recording, 32 preamplifiers with a gain of 1,000 and frequency bands of 5–4,000 Hz were used. After amplification, the signals were fed to a 32-input multiplexor and digitized by an analog-digital converter with 8-bit resolution. A sampling rate of 200–400 Hz was used and 32 digitized electrograms recorded during up to 10 seconds were stored in a 64-kByte buffer and processed by a microcomputer for determination of the moments of activation (−dV/dt max) on electrograms. An arbitrary electrogram could be traced on paper by a chart recorder and displayed on a storage oscilloscope. Before maps of excitation propagation were built, the original electrograms were displayed on a special graphic monitor for correction of local activation times. Corrected data of activation times were used to generate maps of cardiac impulse propagation, namely, isochronal lines representing subsequent positions of the excitatory wavefront. Isochronal lines were built by linear interpolation between sets of three adjacent recording sites showing activation, either automatically or manually. Decrease of conduction velocity below 2 cm/sec was regarded as conduction block. The lack of activation of electrodes under vagal influence (see
As a time interval from cessation of vagal stimulating time) in the pacing experiments was determined to prolong the effects of vagal stimulation. The nerves were stimulated by trains of rectangular voltage pulses via bipolar stimulating electrodes with an interelectrode distance of 1 mm, isolated from ground. Pulse width was 1 msec. In each experiment, stimulation amplitude and frequency were chosen as follows: the frequency of stimulation was first set at 10 Hz and then 5-second bursts of stimulation were repeated with the voltage being increased from 1 V until marked slowing or arrest of sinus rate could be seen. The final value was in the range of 2–15 V. The frequency was then shifted to a value that affected sinus rate to the greatest extent (final value, 10–20 Hz). The chosen values of amplitude and frequency of nerve stimulation were held constant throughout the experiment, and the strength of the stimulation was further regulated only by alteration of the duration of stimulation. Therefore, the term ‘strength of stimulation’ in this report is equivalent to the ‘duration of stimulation’.

In each experiment, the duration of stimulation was gradually increased from 1 to 10 seconds in 0.5–2-second steps. At each step, the electrograms were recorded for 3–10 seconds immediately after cessation of vagal stimulation. The data were stored in computer memory for analysis and generation of maps. Automatically built maps could be obtained on the graphic display several minutes after the electrograms were recorded. If the maps did show areas of vagally induced block and/or reentry we repeated the nerve stimulation at the same strength and/or frequency. If the first set of five or six trials of strong nerve stimulation failed to induce reentrant tachycardia, it was sometimes repeated with longer duration of stimulation. Total number of trials was limited by vagal fatigue, obviously occurring in the later stages of many experiments.

In five experiments, a bipolar Teflon-coated electrode (interelectrode distance, 0.2 mm) isolated from the ground wire was used for atrial pacing to determine the dynamics of restoration of conduction after cessation of vagal stimulation. Atria were stimulated by rectangular current pulses with amplitude of 1.5 thresholds and duration of 3 msec. In these five experiments, proserine (2 mg/l) was added to the perfusate to inhibit tissue cholinesterase activity and to prolong the effects of vagal stimulation.

Duration of excitability restoration (the unblocking time) in the pacing experiments was determined as a time interval from cessation of vagal stimula-
Figure 2. The phenomenon of vagally induced rapid tachycardia in frog atria. At the top, an atrial electrogram during two different trials of vagal stimulation in one experiment is represented. While weaker vagal stimulation led to transient depression of sinus rhythm (upper tracing), stronger stimulation induced rapid tachycardia (lower tracing). Values of the nerve stimulation were as follows: voltage, 11 V; frequency, 15 Hz; pulse duration, 1 msec. Arrows under the electrograms indicate intervals of vagal stimulation. SB, sinus beats; T, episode of tachycardia. At the middle, atrial excitation maps during normal rhythm and the tachycardia are displayed. Electrode grid 10x5 mm. Isochrons indicate the position of activation wavefront at corresponding moments marked near the isochrons (in msec). During sinus rhythm (left), there was regular spread of the impulse from the sinus venosus to both the right and left atria, no areas of depressed conduction being seen. The site of the earliest atrial activation is indicated by 5-msec isochron. During the tachycardia (right), the radial pattern of atrial activation was replaced by circus movement of excitation around a small central area of block (stippled oval). Conduction was slowed and there had appeared another blocked area (thick bars) in the upper part of the right atrium. Isochrons are drawn at 40-msec intervals. At the bottom, unipolar electrograms from four adjacent recording sites indicated on the maps are displayed. From these electrograms the continuous excitation during arrhythmia can be seen. In contrast, during sinus rhythm, the area of the future circuit was excited almost synchronously and did not show any abnormalities in conduction. Broken lines indicate the time window selected for generation of arrhythmia map.

Nonuniform Depression of Conduction Induced by Vagal Stimulation

Figure 3 shows that the conduction pattern in an isolated atria depends on the duration of vagal stimulation and the time after its termination. In one experiment, we made two sequential trials of vagal stimulation: a weak stimulation (duration, 3 seconds) and a strong stimulation (duration, 6 seconds). Activation maps were obtained for a control sinus beat (A), the first sinus beat after the weak stimulation (B), and the first three beats after cessation of the strong vagal stimulation (C1–C3). An increase in vagally induced depression of conduction can be seen by comparison of maps A, B, and C1. While spread of the impulse was regular in the control (A), it was unevenly slowed (predominantly in the medial
part of the atria) after the weak vagal stimulation (B) and was completely blocked in the same area after the strong vagal stimulation (C1). Maps C1–C3 demonstrate restoration of conduction after the strong nerve stimulation. The initially blocked area (C1) became smaller by the arrival of the second impulse (C2), and the third sinus impulse could excite all the atria, although conduction remained somewhat depressed in the formerly blocked zone (C3). However, the fourth sinus impulse after the strong vagal stimulation showed a normal spread over the atria (quite similar to the control). Absence of activation waveforms on the selected electrograms displayed in Figure 3 clearly show inexcitability at corresponding recording sites during either beat C1 only (the site marked by the filled circle) or during beats C1 and C2 (the site marked by the filled triangle). During beat C3, however, activation complexes were of good quality on all of the electrograms. We interpreted this as a restoration of excitability at all of the recording sites by that moment.

Figure 3 shows that after strong enough vagal stimulation conduction into certain parts of atria can be completely blocked for several seconds. Unblocking of the inexcited zones can be asynchronous. To observe the dynamics of the unblocking with higher time resolution, we performed rapid atrial pacing in five experiments, initiated at the moment of cessation of vagal stimulation. A cycle length of 500–600 msec was chosen for pacing to ensure that atrial refractoriness would not influence the activation sequence. The pattern of restoration was rather complex, as can be seen from a representative example (Figure 4).

A bipolar electrode for atrial pacing was placed in the lower left corner of the preparation. To obtain a control map (A), a single impulse was applied to the myocardium just before the nerve stimulation. Immediately after vagal stimulation, the whole right atrium and a part of left atrium were blocked, whereas in the rest of the preparation conduction velocity was only slowed (B). The block can be clearly seen from
FIGURE 4. Dynamics of restoration of conduction in atria after strong vagal stimulation elucidated by atrial pacing at cycle length of 600 msec. In the center, the position of the pacing electrode relative to the mapped area is shown. At the bottom, unipolar electrograms from recording sites indicated by closed circles on map A. It can be seen that on cessation of vagal stimulation (downhead arrow below the electrograms) conduction to the most of the selected recording sites was blocked (beat B). These sites became excitable only some 3 seconds later. However, the activation of the fifth and later the sixth electrodes was retrograde (beats C and D). Beats E and F showed sequence of activation close to control except for somewhat delayed conduction. Activation maps during selected paced beats (A–F), displayed in a circle, show the recovery process in detail. Electrode grid 10×5 mm. Activation times are referred to the moment of corresponding stimulus. Isochron lines are drawn at 40-msec intervals. Before vagal stimulation the excitation pattern was quite regular (A). On cessation of vagal stimulation (B), conduction was slowed in the left atrium and completely blocked in the right (stippled area). Unblocking was started some 3 seconds later (C) and was highly irregular (D and E). Solid black arrow points to a site, where intra-atrial conduction circuit was nearly closed (D), but further unblocking abolished this pattern (E). It was only 4.2 seconds after termination of vagal stimulation that all the sites of the atria were excitable (F).

The selected electrograms displayed in Figure 4. In fact, electrodes 2–6 did not show any sign of activation on cessation of vagal stimulation. The activation pattern was maintained throughout the next three beats (second to fourth stimuli), but during the fifth beat, the impulse was conducted
through a narrow (less than 2 mm) excitable path from the upper right margin of the preparation to the lower right atrium (C), which can also be seen from the electrograms. Subsequent impulses revealed an uneven pattern of restoration, with invaginations and corridors scarring the abating blocked zone (D and E). During the sixth stimulated beat (D), conduction was blocked in the lower medial part of the preparation (indicated by solid black arrow) in an antegrade direction and then (280 msec later) in a retrograde direction. Map D suggested a nearly circular pattern of activation (in fact, one step from complete reentry). However, block at this site had disappeared by the arrival of the next impulse (map E), enabling antegrade conduction and thus abolishing circus movement. This sharp change in activation sequence is apparent from analysis of the electrograms when beats D and E are compared. Finally, during the eighth impulse of the train (F), the excitation pattern approached control and only somewhat depressed conduction was suggestive of vagal action. Activation pattern was restored completely some two seconds later (not shown).

In each of the pacing experiments, we repeated the same stimulation protocol after administration of proserine (2 mg/l), an inhibitor of cholinesterase, and found that this substance markedly slowed the dynamics of the restoration of excitation pattern. Figure 5 shows maps of three selected stimulated impulses from the pacing protocol after administration of proserine in the same preparation as in Figure 4. On cessation of vagal stimulation, the pattern of blocking was similar to that in the absence of proserine (compare Figures 4B and 5A). The activation pattern was stable throughout one to seven impulses, but the eighth impulse passed from the upper right border of the preparation to the lower right atrium (Figure 5B), similarly to Figure 4C. The further unblocking of the inhibited area under proserine (not shown) resembled that in the absence of proserine, but its time course in the former case was much slower. Only the 13th impulse (Figure 5C) excited all the atria. This suggests that under proserine complete unblocking of the inhibited zone was delayed by 3.0 seconds (70%) as compared with proserine-free case.

Under proserine, conduction of stimulated impulses was progressively delayed in the vicinity of the atrial pacing electrode (the lower left corner of the preparation, see Figures 5B and 5C). This effect was negligible in absence of proserine. Progressive increase of conduction time in the vicinity of atrial pacing electrode was possibly due to local release of acetylcholine, induced by direct stimulation of intracardiac nerves. Proserine probably have enhanced this effect due to inhibition of cholinesterase, leading to accumulation of locally released acetylcholine. In one of five pacing experiments, continuous atrial pacing under proserine elicited complete exit block of stimulated impulses (not shown). Although this side effect of atrial pacing made the observed pattern of the restoration more complex, it seemed to be restricted to a small area close to the stimulating electrode and did not appear to influence the dynamics of the unblocking in the rest of atria. These dynamics were most likely determined by the rate of elimination of acetylcholine released during vagal stimulation. In four of five pacing experiments (the fifth one was excluded

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**Figure 5.** Slowing of the recovery from vagal blockade under proserine administration (2 mg/l), in the same experiment as in Figure 4. At the top, activation maps for selected paced beats are displayed. While the shape of the blocked area on cessation of vagal stimulation (A) was quite similar to that of Figure 4, its recovery was delayed under proserine administration. The unblocking began only 4.2 seconds after vagal stimulation ceased (B) and was finished by 7.2 seconds (C) after termination of vagal stimulation. Marked slowing of conduction in the lower left corner of the preparation (close to the pacing electrode) may be caused by local release of acetylcholine, induced by direct stimulation of intracardiac nerves. At the bottom, moments of the selected beats are shown on the electrogram from recording site, indicated by filled triangles on the maps.
because of exit block of stimulated impulses developed under proserine), the unblocking time was 3.9±0.7 before and 6.9±1.0 after administration of proserine. The difference was statistically significant (p<0.05).

Atrial pacing experiments revealed high variability of the size and location of vagally blocked zones. Unblocking of these zones usually featured a complex mosaic pattern, which was not completely reproducible in successive repeats of the postvagal pacing. Certain patterns of the unblocking led to reentrant excitation, as will be shown in the next paragraph.

**Circus Movement of Excitatory Wave in Frog Atria After Relief of Vagally Induced Conduction Block**

A detailed mapping of such a tachycardia is represented in Figure 6. Before vagal stimulation, the sinus impulse activated the atria in a regular manner at an average rate of 9 cm/sec (A). The conduction pattern of the first sinus impulse after vagal stimulation was significantly different (B1 and B2). The conduction was slowed (approximately twofold) in the right atrium and blocked in the lateral part of the left atrium (B1). The impulse entered the formerly inexcited area 165 msec after the beginning of atrial activation and was conducted through this area in a retrograde direction (B2). It reached the sites distal to the area of primary block in lower left part of the preparation and, after a delay, reentered the atria. Since the sites proximal to the area of primary block had been excited about 400 msec earlier, the wavefront could reexcite them, resulting in initiation of circus movement of the wavefront. This conduction pattern was maintained throughout several beats of the tachycardia (C). The shape of the area of the central block did not change and the time of revolution of the wavefront remained close to 400 msec. In each cycle, propagation of the impulse was beyond the scope of mapping during 150 msec (about 40% of the cycle length). However, the missing part of the circuitous pathway was most likely small since the width of unmapped area along the margins of the preparation was not greater than 2 mm. Consequently, conduction of the impulse in the hidden part of the intratrial circuit should be very slow. However, the possibility cannot be excluded that the sinoatrial junction, which was close to this area, was involved in the circus movement in this particular case.

The conduction pattern was significantly changed during the next to last beat of the arrhythmia (D). First, the perimeter of the reentrant circuit was markedly shortened (to about 8 mm), and the revolution time abruptly fell to 250 msec, or about 63% of the initial value. The sequence of activation suggests a short circuit of the reentrant pathway across the upper medial part of the primary area of block (D). Second, some additional areas of block could be seen. We called them "secondary blocks" as distinct from "primary blocks," which occurred before initiation of the circus movement. Since the secondary blocks appeared when the cycle length of the tachycardia abruptly decreased, they might reflect the fact that in some areas the refractory period is longer than the shortened cycle length. During the last beat (E), the circus movement was interrupted by an increased area of secondary block, probably as a result of the gradual prolongation of the refractory period by recovery from vagal inhibition. The original electrograms, represented on Figure 6, show the sequence of excitation along the reentrant circuit. The exact electrode positions are indicated on map A. Unlike sinus rhythm, the arrhythmia electrograms show continuous excitation. Recording site 2 is activated more frequently than others. This phenomenon resembles "double potentials" previously reported by Allessie et al that "were found at sites where two limbs of a circuitous pathway were in close apposition." These authors postulated that "electrodes positioned exactly on the line between two oncoming activation waves can 'see' both waves passing along at either side." Therefore, the "double potentials" at the electrogram No. 2 possibly indicate that the blocked area was very thin at this site (see "Discussion").

Unlike the cases illustrated in Figures 2 and 6, some episodes of reentrant excitation around the central area of block suggested that the region was of considerable size and apparently "two-dimensional" so that some central recording sites were continuously unexcitable. In such cases, gradual abatement of the central blocked area was observed during the tachycardia. An example of this is presented in Figure 7. The maps of the excitation pattern during all seven beats of an episode of vagally induced tachycardia (A–G) together with control map (H) are displayed. The pattern of conduction during this arrhythmia was very complex, so we will consider only the principal features of it. After vagal stimulation, the sinus impulse was blocked in the right atrium while being conducted over the left atrium and very slowly around considerable area of block along upper and right margin of the preparation (A). The excitatory wave reached the lower right atrium, and 110 msec later, reexcited the sites in the left atrium, which had been excited by the sinus impulse 455 msec earlier. The pattern of activation suggests circus movement of the impulse, although major parts of the reentrant circuit (along upper and lower atrial borders) could not be defined (shown by broken arrows). During subsequent beats of the tachycardia (B–G), a marked evolution of the circuitous pathway and pattern of blocking was observed. The primarily blocked area abated part by part, being sometimes divided into separate islets by conductive corridors. Finally, the estimated size of the reentrant circuit became as small as 6 mm. On the other hand, some new (secondary) blocks developed in peripheral regions of the atria. These new blocks arose every second beat of the arrhythmia, indicating that corresponding
FIGURE 6. Circus movement of the excitatory wave originating from sinus venosus during recovery from vagal inhibition. At the top, activation maps during initiation (B1 and B2), stable phase (C), and termination (D and E) of the vagally induced tachycardia are presented, together with control map (A). Electrode grid, 10×10 mm. Isochrons are drawn at 50-msec intervals and labeled by serial numbers, except for Panel A where activation times are indicated in milliseconds. On Panel B, the 0-isochron corresponds to 15-msec instant of atrial activation. After vagal stimulation, propagation of the sinus impulse was blocked in the left atrium (stippled area) and slowed in the rest of the atria (B1). Sites distal to border of the initial block were activated retrogradely, and then the impulse reentered the atria (B2), with part of the reentrant circuit being unmapped (broken arrow). The established reentrant circuit was unchanged during the next five beats (C), until the circulating impulse was "short-circuited" across the primarily blocked area (D). This was followed by "secondary" blocks of conduction (thick bars) in some sites. During the last cycle (E), a considerable conduction block appeared in the right atrium, and the tachycardia was abruptly terminated. At the bottom, selected unipolar electrograms, covering the reentrant circuit, are displayed. Corresponding recording sites are indicated on Panel A. Time windows above the electrograms show the intervals over which sequence of activation was detected for corresponding maps. The second electrogram features double activation during some cycles, which may reflect the central position of the corresponding recording electrode in the area around which the impulse circulates.
sites could not assume the high rate of the tachycardia. The conduction velocity was not uniform along the circuitous pathway. The cycle length fluctuated during the arrhythmia (see electrogram in Figure 7). Such fluctuations could be a result of some unstable interactions between the crest and the refractory tail of the wave caused by continuous change of electrophysiological parameters of atrial tissue during the recovery process (see "Discussion").

During the seventh beat (G) the conduction was abruptly blocked in the lower right atrium, and tachycardia ceased. The conduction block could be connected with sharp acceleration of conduction during this beat that might have led to the running of the wavefront against the elongated refractory tail. The first sinus beat after cessation of tachycardia (H) showed normal excitation.

The next trial with the same strength of vagal stimulation led to another episode of tachycardia (not shown) that was similar to the first one shown in Figure 7. Average cycle length of tachycardia was close in the two cases. Activation sequence during the initial beat of the second episode was much alike that of the first episode (Figure 7B), but during consequent beats, the evolution of the circuitous pathway was somewhat different, particularly, unblocking of the central inexcitable area was delayed in the second case. Duration of the second paroxysm was also longer and consisted of nine cycles (two cycles more than the case shown in Figure 7). In
other experiments in which more than one episode was obtained, the pattern of the tachycardia also was not completely reproducible. The cycle length, duration, and pattern of the circus movement usually were similar in different episodes of the arrhythmia.

**Discussion**

A crucial role of cholinergic influence in rapid atrial tachycardias has been noted both by physiologists and clinical investigators. This role is commonly related to nonuniform shortening of atrial refractoriness, which increases a probability of circus movement of a premature excitation. Since the origin of a primary premature excitation is unclear, some other mechanism of cholinergic atrial tachyarrhythmia independent of primary extrastimulation can be of interest.

Such a mechanism was suggested to explain tachycardia secondary to vagal stimulation in frog atria. The authors found that it was linked with vagally induced inexcitable zones. They postulated that instantaneous restoration of excitability in a blocked zone could lead to reentrant excitation if it took place during a certain phase of atrial activation. This is schematically represented in Figure 8. While the wave spread radially during control conditions (A), after vagal stimulation it is blocked at the border of the vagally blocked zone (B) and begins to turn around it (C). If part of the inexcitable zone abruptly becomes conductive (D), the wavefront is able to reexcite the sites proximal to the blocked zone. In such a way, circus movement is established without involvement of an anatomic obstacle (D). The hypothesis can be briefly expressed as follows: temporary vagally induced inexcitable zones lead to reentrant excitation, serving as a site of unidirectional conduction.

The present mapping study gives strong evidence for the suggested mechanism of vagus-dependent tachycardia in frog atria. In fact, maps of activation during the tachycardia clearly showed a reentrant pattern of activation (Figures 2, 6, and 7). We observed that initiation of the arrhythmia was always preceded by inexcitable areas, often of considerable size (Figure 7). Arrival of the sinus impulse at a critical time, namely, at a certain phase of unblocking of the vagally blocked zone so that this zone provided unidirectional conduction, resulted in the circus movement of the impulse in atria.
In the theoretical considerations that somewhat inspired this study, conduction velocity was not considered to be affected by vagal influence. However, our data showed that vagally induced slowing of conduction played an essential role in initiation and maintenance of the circus movement. Slow conduction velocity was related to sites with rather low strength of vagal influence (Figure 3B) and/or sites with incomplete recovery from vagal influence (Figure 3, C2, and C3, and Figure 4E and F). Under vagal influence, conduction velocity could fall to as low as 2–3 cm/sec, or three to five times lower than under control conditions. Along with drastic shortening of the action potential duration, this allowed reentrant circuits with diameters of about 2 mm to occur (Figures 2 and 6).

Circus movement tachycardia in rabbit, dog,2,5 and frog atria was induced by rapid pacing or application of a properly timed premature impulse to atrial myocardium. This was not the case in our experiments. Instead, we stimulated vagal nerves and after that the first sinus impulse after a pause of sinus arrest was sometimes followed by a paroxysm of reentrant tachycardia. Hence, the major difference between our model and others is the mechanism of initiation of the circus movement, namely, the mechanism of unidirectional block of conduction. In models with programmed atrial stimulation, the site of unidirectional conduction was predominantly determined by nonuniform distribution of refractoriness in atrial tissue, whereas in our model this site was determined by vagally induced nonuniform blocking of conduction. This arrhythmogenic effect of enhanced vagal tone seems to be independent of vagal effects on atrial refractoriness.11,12 Irregular distribution of vagal effects may be due to variable density of nerve terminals and/or muscarinic receptors in different regions of atria.

The second difference of this model from others is that in our model initiation and pattern of reentrant tachycardia were much less stable and reproducible. It can be explained by the fact that the reentrant tachycardia in our experiments was initiated during a period of the postvagal recovery that was characterized by highly unstable electrophysiologic parameters. Excitability and conduction velocity were rapidly changing during the recovery. Unblocking of vagally induced inexcitable zones was as a rule asynchronous and could have complex dynamics (Figure 4). In each preparation, the unblocking pattern was similar in successive trials of vagal stimulation, but the details of it were unpredictable. However, these details determined whether or not the circus movement would be initiated. That is why induction of tachycardia by vagal stimulation was not always reproducible in our experiments. Once induced, the reentrant pattern could be changed dramatically during the arrhythmia (see Figures 6 and 7). Unlike other models, in which the cycle length was either stable or gradually increasing,1 in our model it usually got shorter as the tachycardia progressed. This shortening (Figure 6) of the cycle length was probably due to abatement of the central vagally induced "obstacle" around which the impulse circulated, as a result of recovery from vagal action. If the perimeter of the "obstacle" (P) is initially greater than the wavelength of the circulating impulse A = R × V (R, length of refractory period, and V, velocity of conduction), the cycle length (T) is equal to P/V. Consequently, if P decreases but V does not, the cycle length will be shortened as long as P is still greater than RV. The decrease of the cycle length time can be abrupt if the circulating impulse is "short-circuited" by a "conductive corridor" crossing the central blocked zone.14 Such "corridors" were frequently observed during the recovery following vagal stimulation (Figures 4, 6, and 7), and the short-circuit of the circulating impulse seems to be a plausible explanation for abrupt acceleration of the tachycardia, as shown in Figure 6.

Occasional beat-to-beat variations of the cycle length were also observed in our experiments (Figure 7). This probably results from some complex interactions. According to the above considerations, the perimeter of the central inexcitable "obstacle," P, may be reduced as the vagal effects decrease, as will the cycle length, as long as P is greater than RV. At the same time, as the vagal effects decrease, the duration of atrial refractoriness, R, will increase. Both reduction of P and increase of R will eventually lead to disappearance of an excitatory gap between the crest and the tail of the impulse (P=RV). This might result in reduction of the "excitability" of the wavefront and, consequently, a slowing of conduction which in turn will lead to increased cycle length. However, as the vagal effects further decrease, the stimulating efficacy of the impulse might increase, and this will result, once again, in shortening of the revolution time of the circus movement.11 Such a state of unstable interactions between the crest and the tail of the wave might persist until the end of the tachycardia, resulting in fluctuations of the cycle length.

Nonuniformity of recovery of atrial refractoriness after vagal stimulation10 increased instability of the intra-atrial circus movement. While the refractory period in slightly depressed areas can be much longer than in strongly depressed areas (in which the circulating impulse exists), the former may not always be involved in the high rate of the tachycardia. Instead, "secondary" blocks develop, resulting in transformation of rhythm in these areas with the ratio 1:2 or even 1:3 (Figure 7).

The pattern of each episode of reentrant tachycardia was somewhat unique; that is, other episodes of tachycardia in the same preparation were similar, but never quite the same, even for the same parameters of vagal stimulation. This may be also a consequence of stochastic character of restoration
of electrophysiological parameters in frog atrial tissue after strong vagal stimulation.

Another distinctive feature of our model seems to be the nature of the central area, around which the impulse circulates. In other models, two main types of reentry were defined: with and without the involvement of a central anatomical obstacle. The first type of reentry is characterized by the fixed length of the circular pathway, determined by perimeter of the anatomic barrier (P). The cycle length, T, is equal to P/V, and there is usually an excitable gap between the crest and the tail of the circulating impulse. The second type of reentry was defined in early theoretical works as "circulation around a segment,"27 or "reverberator."12 and now the term "leading circle"11 is most widely accepted. It is characterized by the absence of an excitable gap between the front and the tail of the wave, so that the perimeter of the circuit is equal to the wavelength of the impulse (P=RV) and the cycle length is determined by duration of the refractory period (T~P).

In our experiments, we observed a vagally induced "barrier" of an intermediate type in the center of the circuitous pathway. This intermediate barrier is functional and not anatomic (similar to "leading circle" type), but provides an excitable gap in the reentrant cycle (like an anatomic obstacle).27 Because of continuous abatement of the central vagally induced "obstacle," the reentrant circuit might become of a pure leading circle type at a late stage of the tachycardia (see Figure 8, E-F). This is supported by observation of "double potentials" on some electrograms, for example, double activation of electrodes during one tachycardia cycle (see Figure 6), which might indicate that these electrodes are close to the center of the leading circle.3

Duration of reentrant supraventricular arrhythmias was highly variable, ranging in different models from a single extra beat28 to sustained tachycardias that lasted for many hours.5 In our model, paroxysms of tachycardia were short (not longer than 5 seconds), probably because the reentrant circuit could exist in such a small preparation (within 10×10 mm) only when the wavelength of the cardiac impulse (RV) was greatly reduced. Since R and V increase as vagal effects decrease, the duration of the tachycardia should be limited by the duration of the postvagal restoration. The time course of the recovery was determined largely by the rate of elimination, by tissue cholinesterase, of acetylcholine released during vagal stimulation. Therefore, administration of proserine delayed the recovery (compare Figures 4 and 5) and prolonged the duration of the arrhythmia (not shown).

In earlier studies, acetylcholine-induced conduction blocks were observed in frog auricle and tortoise sinus venosus,22 in sinoatrial and atrioventricular node of mammalian hearts,29,30 and in subsidiary pacemakers of canine right atrium.31 Considerable increase of outward potassium current by acetylcholine32 may exert block due to a decrease of net inward current during the upstroke of the action potential. On the other hand, acetylcholine-induced inhibition of the slow inward current might be responsible for depression of conduction in tissues in which the action potential is predominantly the slow response, for example, in nodal tissues.29,30 We cannot exclude the possibility that the suggested mechanism of cholinergic reentrant tachycardia may be responsible for some supraventricular tachycardias in mammalian hearts, particularly those involving sinus or atrioventricular nodes.2 Nonuniform depression of conduction induced by vagal influence in nodal tissue30 might lead to intranodal microneurograms similar to that induced by extrastimulation.28,34 However, these assumptions need experimental support.

References


**KEY WORDS** • atrial tachycardia • reentry • vagally induced block • activation maps