An In Vitro Model of Paroxysmal Supraventricular Tachycardia

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SUMMARY
An in vitro preparation of rabbit right atrium, including the A-V node (AVN) and bundle of His, was utilized to evaluate the mechanism of paroxysmal supraventricular tachycardia (SVT). Microelectrode recordings from atrium and AVN were obtained. During sinus rhythm the atrial cycle was explored with atrial premature depolarizations (APD). Fifty episodes of an arrhythmia with characteristics identical to SVT in man were produced in six of 40 rabbits. In vitro, SVT: (1) was initiated by a single APD showing prolonged conduction in the AVN; (2) had initial cycles similar to atrial echoes; (3) in most instances showed 1:1 A-V conduction; (4) lasted 20 to 500 cycles; and (5) could be ended by a single APD which penetrated the AVN. Reentry in the upper AVN was established by the recording of action potentials from nodal cells which showed marked electrotonic "humps" during repolarization. SVT and atrial echoes could not be produced after damaging or sectioning the upper AVN. An in vitro model of SVT supports the hypothesis that this arrhythmia results from reentry within the AVN.

Additional Indexing Words:
Atrial tachycardia Reentry Premature atrial depolarizations A-V node Microelectrode

The mechanisms underlying clinical cardiac arrhythmias are of considerable significance, since knowledge of these processes may provide a basis for successful therapeutics. Unfortunately, these arrhythmias are not easily studied in clinical situations. As a result, conclusions concerning their origin have been largely speculative, and based on electrocardiographic analysis. This has been particularly true with regard to the genesis of paroxysmal supraventricular tachycardia (SVT) in man. Two prevalent but antithetical views regarding the mechanism of this arrhythmia can be found in the literature. One view asserts that paroxysmal supraventricular tachycardia is due to a rapidly firing ectopic pacemaker in the atrium, or atrioventricular (A-V) junction. The other adheres to the concept that SVT is the result of atrial reentry involving either the sinoatrial (SA) or A-V nodes or possibly both. Recent detailed experimental studies in man by Bigger and Goldreyer provide evidence that paroxysmal supraventricular tachycardia does, in fact, result from continuous reentry through the A-V node.

Replication of clinically encountered cardiac arrhythmias in the experimental animal, either in vivo or in vitro can provide a more direct and accessible means of studying their mechanisms. We have produced an arrhythmia identical to clinical paroxysmal supraventricular tachycardia in the isolated perfused...
rabbit right atrium. This preparation allowed detailed investigation of the mechanism of SVT with local electrograms, glass capillary microelectrodes, and various degrees of tissue sectioning. These techniques have directly demonstrated that SVT is initiated and sustained by reentry within the upper A-V node.

Methods
Rabbits weighing 2–3 kg were instantly killed by a swift blow to the head. The sternum was rapidly removed and the entire heart dissected free and placed in a modified Tyrode's solution of the following composition (millimolar): NaCl, 137.0; KCl, 3.0; NaH2PO4, 1.8; CaCl2, 2.7; MgCl2, 0.5; dextrose, 5.5; and NaHCO3, 12.0. Subsequent dissection was performed in this Tyrode's solution which was gassed with a mixture of 95% O2 and 5% CO2. The ventricles and left atrium were removed and discarded. The endocardial surface of the right atrium was exposed by an incision through the free wall at the atrioventricular groove, extending along the anterior border of the right atrial appendage and through the anterior wall of the superior vena cava as described in detail by Paes De Carvalho et al. The preparation consisted of the superior vena cava, sinus node, crista terminalis, musculi pectinati of the atrial appendage, interatrial septum, coronary sinus, A-V node, and bundle of His. The exposed endocardial surface of the right atrial preparation was pinned to the wax base of a 20-ml tissue bath and constantly perfused with the Tyrode's solution, gassed with 95% oxygen and 5% carbon dioxide. Temperature was maintained at 34–36°C. The spread of excitation during sinus rhythm was verified to occur in a normal manner before study was initiated.

Transmembrane action potentials were recorded by means of machine-pulled glass capillary microelectrodes filled with 3M KCl (tip resistance of 20–40 meqomhs). The microelectrodes were coupled to the input circuits of high input impedance amplifiers with capacitance neutralization (type NF-1, Bioelectric Instruments, Inc.) (two identical assemblies) by means of Ag-AgCl wires. The outputs of these amplifiers were displayed on two oscilloscopes (Tektronix 565 and 532). Action potentials were recorded from the crista terminalis or atrial muscle in the vicinity of the A-V node, from the upper (AN), middle (N), or lower (NH) regions of the A-V node, and from the bundle of His. Regions within the A-V conduction system were identified according to action potential configuration and timing as previously described. The site or sites of recording for individual experiments varied and are indicated in the results.

In addition to the transmembrane action potentials, bipolar surface electrograms were recorded from atrial muscle in the vicinity of the A-V node, and in some experiments from the His bundle by means of Teflon-coated silver wires. Electrograms were displayed along with the action potentials. A calibrated time signal provided by a time-mark generator was similarly displayed. Direct current calibration pulses were injected into the bath via ground for calibration of resting potentials and action potential amplitudes. Photographic records were obtained on moving film by means of a Grass C4-oscillographic camera.

The preparation beat spontaneously and was driven by its own sinus pacemaker. The bipolar atrial electrogram was used to trigger the "A" time base of the 565 oscilloscope and the sweep speed adjusted so that one complete sweep encompassed 10–15 sinus beats. The "A" time base was also used to trigger a second ("B") time base generator with a variable delay. The gate from the "B" time base was used to drive a Tektronix 160 series wave form and pulse generator which delivered an isolated stimulus (5 msec in duration, 4–5 × threshold) to the right atrium through a pair of bipolar silver wire electrodes on the crista terminalis. Thus, the preparation could be stimulated once during each complete sweep of the A beam (every 10–15 beats) and the premature stimulus placed at any point in the cardiac cycle with an accuracy of ±1 msec.

Results
The effects of stimulated premature atrial depolarizations on atrial rhythmicity was studied in 40 rabbit right atrial preparations. The entire sinus cycle was explored by progressively decreasing the coupling interval between the premature atrial depolarization (Ap) and the atrial depolarization of sinus origin (As) by intervals of 5 msec or less. In six preparations a single premature stimulus induced a series of rapidly occurring regular atrial depolarizations lasting from 20 to 500 cycles (fig. 1). This supraventricular tachycardia could be repeatedly induced by appropriately timed atrial premature stimuli, and a total of 50 such episodes were studied.

General Characteristics of Induced Tachycardia
As the premature response (Ap) was evoked progressively earlier in the sinus cycle
Supraventricular tachycardia in rabbit right atrium. Upper action potential recorded from atrial muscle fiber within 4 mm of A-V node. Lower action potential recorded from cell in N region of A-V node. Numbers listed above are atrial cycle lengths in msec, numbers below are conduction times from atrial muscle fiber depolarization to A-V nodal fiber depolarization in msec. Time pips on top trace represent 20-msec intervals; voltage calibration to the left is 100 mv. (Panel A) First two atrial depolarizations are of sinus origin (sinus cycle length 585 msec). Conduction time from atrium to N region is 53 msec. A premature atrial depolarization (arrow) in induced 130 msec after the last sinus impulse and conduction time to the N fiber is 118 msec. This premature atrial depolarization initiates a rapid tachycardia lasting 210 cycles. Alternations in atrial cycle lengths and A-V nodal conduction times of the first five depolarizations of the tachycardia are shown in the remainder of panel A. (Panel B) Atrial depolarizations numbers 70–78 in the atrial tachycardia. Atrial cycle length is now constant despite slight variation in conduction time to N cell. (Panel C) Last four atrial cycles before spontaneous termination of tachycardia. Atrial cycle lengths again vary as does atrial-nodal conduction time. Tachycardia terminates within the A-V node. Note the long pause before sinus rhythm is restored, most likely due to post over-drive depression of the sinus node.

(As), an As-Ap interval was reached where it would induce one to three rapid atrial depolarizations (atrial echoes) prior to the resumption of sinus rhythm. This As-Ap interval fell within the relative refractory period of the A-V node and was outside the relative refractory period of atrial muscle. When a stimulated premature atrial depolarization was evoked slightly earlier, in the A-V nodal relative refractory period, a tachycardia was initiated (fig. 1).

During the initiation of atrial echoes and tachycardia, the interval between the last sinus impulse and the premature atrial depolarization was reciprocally related to the following cycle length (between the premature atrial depolarization and subsequent atrial response. [A3]). As the coupling interval of the premature depolarization inducing both atrial echoes and tachycardia was shortened, the subsequent atrial cycle length prolonged in a linear fashion (fig. 2). This reciprocal relationship indicates that the first atrial impulse in the tachycardia (A3) is an echo beat induced by the premature atrial depolarization (also, see fig. 6).8

In all episodes of tachycardia the initial five to ten atrial cycles were characterized by an alternation of variably longer and shorter cycles (fig. 1A) before a stable cycle length was achieved (fig. 1B). This constant atrial cycle length ranged from 180–216 msec in
IN VITRO MODEL OF PAROXYSMAL SVT

Figure 2

Reciprocal relationship between As-Ap interval (interval between last sinus impulse [As] and premature atrial depolarization [Ap]) and the Ap-A3 interval (interval between Ap and the subsequent atrial response [A3]) during the initiation of atrial echoes (●) and supraventricular tachycardia (○).

different preparations, but was identical for all tachycardias in a single preparation.

There was 1:1 A-V conduction from atrium to bundle of His during the tachycardia in all but four of the 50 episodes produced. In these latter instances different degrees of A-V block, varying from 2:1 to Wenckebach periodicity, occurred. When the tachycardia terminated spontaneously an alternation of atrial cycle lengths resumed five to ten cycles before the tachycardia terminated (fig. 1C). Sinus rhythm was restored after a long escape interval. At the initiation of the tachycardia progressive decrease in atrial cycle length was never observed nor was there a gradual increase in cycle length (slowing) at its termination.

Single premature stimuli were introduced throughout the atrial cycle during 10 episodes of tachycardia in three preparations. When the atrial premature depolarization was evoked with sufficient prematurity the tachycardia was immediately terminated in all instances. The atrial tachycardia could also be terminated by driving the atrium at a cycle length slightly shorter than that of the tachycardia for 3–5 sec. A summary of the characteristics of the supraventricular tachycardia in the rabbit right atrium is included in table 1.

Effects of Sectioning Atrial Muscle and A-V Node

Experiments were performed to localize the anatomic region or regions of the right atrial preparation required for the initiation and maintenance of the tachycardia. Incisions penetrating the endocardial surface of the preparation and extending 5–7 mm in length were placed randomly in the atrium. This was without effect in all preparations. Similar lesions placed along the septal and cristal border of the sinus node were also without effect on our ability to initiate tachycardia. These cuts did not interfere with conduction

Table 1

General Characteristics of Supraventricular Tachycardia (SVT)

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<th>Experiment no.</th>
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<tr>
<td>SVT cycle length (msec)</td>
<td>184</td>
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<tr>
<td>No. of SVT's induced</td>
<td>7</td>
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<tr>
<td>AVNERP (As-Ap) (msec)</td>
<td>120</td>
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<tr>
<td>AVNFRP (His-Hp) (msec)</td>
<td>180</td>
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Abbreviations: As-Ap = interval between atrial depolarization of sinus origin and induced premature atrial depolarization; AVNERP = A-V nodal effective refractory period; AVNFRP = A-V nodal functional refractory period; His-Hp = interval between His bundle depolarization of sinus origin and His bundle depolarization of premature impulse.

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of the sinus impulse to the atrial muscle or A-V node. Removal of the entire uppermost one third of the atrium including most of the sinus node in two studies (fig. 3) did not prevent initiation of the tachycardia. (Microelectrode recordings showed cells remaining with typical sinus node action potential configuration.)

The relationship of the proximal A-V conduction system (A-V node and His bundle) to the genesis of this supraventricular tachycardia was similarly investigated in four experiments. A small (3 mm) cut, functionally separating the upper His bundle from the lower A-V node did not alter our ability to produce tachycardia, or the characteristics of the tachycardia once initiated (fig. 3). (Functional separation was documented when action potentials from the His bundle and A-V node showed no temporal relationships.) In striking contrast, the supraventricular tachycardia could never be elicited after a discrete 3-5-mm cut extending along the upper margin of the A-V node had been made. This incision prevented the conduction of atrial impulses into nodal cells (fig. 3). (The upper nodal margin was located prior to sectioning by typical action potential configuration.)

When the A-V node was damaged by slight pressure with a glass rod in one experiment, A-V nodal conduction was impaired and the tachycardia was prevented (fig. 4). In this experiment various degrees of A-V block occurred after A-V nodal damage. Nonconducted atrial impulses were concealed in both the upper and middle A-V nodal regions.

These manipulations involving the A-V node which prevented tachycardia had no discernible effects on the automaticity of the sinus node, or the sinus-to-atrial muscle conduction time. (The interval between depolarization of sinus node cells in a specific region and atrial muscle fibers in the crista terminalis was unchanged.) Damaging or sectioning the A-V node did not alter conduction or the electrophysiologic characteristics of atrial muscle fibers. (Mean values for resting potential, action potential duration, and refractory periods remained unaltered.)

Excision of a large mass of atrial muscle (fig. 3) leaving a small island of atrial tissue surrounding the A-V node, also prevented the initiation of the tachycardia in two preparations. These preparations (after excision) were electrically driven at a cycle length similar to that of the sinus node prior to its removal. Although A-V nodal conduction and A-V nodal functional and effective refractory periods were all unimpaired by this sectioning procedure, tachycardia could not be produced (see discussion).

**Electrophysiologic Characteristics of A-V Nodal Cells During Tachycardia**

The fact that the tachycardia could be prevented by discrete lesions involving the A-V node or atrial A-V nodal junction is prima facie evidence that the A-V node is involved in the genesis of in vitro SVT. This was more fully investigated by recording transmembrane action potentials from A-V nodal cells in the upper (AN), middle (N), and lower (NH) regions of the node during the
initiation and termination of sustained tachycardia. Regions of the A-V node were identified according to the characteristics of recorded action potentials, and their temporal activation relative to atrial and His bundle electrograms.\textsuperscript{11}

As the premature atrial response (Ap) was evoked progressively earlier in the atrial cycle, its transmission through the A-V node became increasingly delayed. When A-V nodal conduction was markedly prolonged the atrium showed a second rapidly occurring depolarization suggesting reentrant excitation.\textsuperscript{12} The A-V nodal conduction time of the first premature depolarization during which reciprocal atrial excitation occurred, marked the beginning of a well-defined echo zone (fig. 5). As Ap was made to occur even earlier in the atrial cycle, its conduction in the A-V node was further delayed and tachycardia was initiated (fig. 6). The A-V nodal conduction times of premature impulses initiating sustained tachycardia demonstrated a very narrow range (no greater than 10 msec for any single preparation). If conduction time in the node was prolonged to a greater extent (as occurred after still earlier premature atrial impulses), only single or multiple atrial echoes occurred (figs. 5 and 6).

The major A-V nodal conduction delay exhibited by premature atrial impulses initiating tachycardia occurred in the upper nodal (AN) region. The increased conduction time between atrial and His bundle electrograms characteristic of atrial premature depolarizations, was accounted for primarily by the increment in conduction time between the atrial electrogram and cells exhibiting action potentials characteristic of the AN region (fig. 7). Only a small increment in conduction occurred between the AN and N or NH regions of the node. (Conduction time between AN and NH cells was not increased by more than 15 msec even when the most premature impulses were compared to sinus beats.)

The characteristics of A-V nodal action potentials during tachycardia are shown in figures 7–10. Action potentials of cells within the upper node (AN region) showed marked changes in configuration after tachycardia was induced. There was a decrease in action potential amplitude. When tachycardia was initiated a marked “hump” immediately developed on the descending limb of the AN action potential and became progressively more pronounced during the initial two to five nodal depolarizations of the tachycardia (fig. 7A). This AN action potential characterized by a “hump” on its descending limb, persisted throughout the duration of the tachycardia in most experiments. In two instances this notching gradually disappeared over the 10 cycles preceding the spontaneous termination of tachycardia. The additional depolarization responsible for the “hump” recorded from AN cells during tachycardia varied in amplitude and position on the descending action potential limb of different cells but it always occurred prior to the next atrial depolarization. That is, both peaks of the action potential occurred within the interval set by two successive atrial depolarizations of tachycardia. When atrial cycle length was varying, for instance, during the initial or terminal cycles of tachycardia, the position of the “hump” on the descending limb of AN potentials also varied (fig. 8). When tachycardia was initiated, during short atrial cycles the “hump” appeared early after repolarization began; during longer atrial cycles it occurred later in repolarization. When the tachycardia assumed a constant atrial cycle length, the amplitude and position of the “hump” became constant. When the atrial cycle length began to alternate again prior to the spontaneous termination of tachycardia, again the “hump” occurred earlier in repolarization during short atrial cycles, and later in repolarization during long cycles (fig. 8). These changes in atrial cycle lengths occurred in many instances without any change in total conduction time from atrium to His bundle.
Atrial tachycardia and atrial echoes induced by premature atrial depolarizations. Upper action potential recorded from N region of A-V node, lower action potential from atrial muscle in the vicinity of the A-V node. Numbers above indicate time intervals from atrial depolarization to nodal depolarization in msec; numbers below are atrial cycle lengths in msec. Time and voltage calibrations as in figure 1. (Panel A) Premature atrial depolarization (arrow) induced 213 msec after the last sinus beat shows delayed conduction into the A-V node (97 msec). (Panel B) Premature atrial depolarization (arrow) induced 145 msec after the last sinus beat is conducted to N cell after 131 msec and initiates a tachycardia which lasted 400 cycles, only first six cycles are demonstrated. (Panel C) A premature atrial depolarization (arrow) at a coupling interval of 136 msec is conducted to N cell after 136 msec and induces two atrial echoes. (Panel D) Premature atrial depolarization (arrow) induced at 130 msec has a conduction time to N cell of 167 msec and elicits only a single atrial echo. The reciprocal relationship between the As-Ap interval and the Ap-A3 interval (see fig. 2) is also demonstrated in panels B–D.

When tachycardia terminated spontaneously, and the last nodal depolarization was not followed by atrial activation (i.e., tachycardia ended in the node), the “hump” did not appear on the terminal AN action potential (fig. 8C).

To demonstrate that the “hump” observed on AN cell action potentials during tachycardia was related to atrial reentry, the atrium was driven at cycle lengths identical to those occurring during the tachycardia. During electrical stimulation there was no “hump” on the upper nodal action potentials (fig. 9). Since we were not successful in maintaining impalement of the same cell during induced tachycardia and the subsequent rapid atrial pacing, action potentials were recorded from from three to five cells within 0.5 mm of one another during tachycardia in three experiments. All these AN cells exhibited “humps.” An additional three to five cells were recorded from the same area during atrial pacing. A “hump” was not evident in any. When the atrium was driven at a cycle length identical to that observed during tachycardia, various degrees of conduction impairment between atrium and His bundle usually occurred, despite the fact that 1:1 atrioventricular conduction was observed during the tachycardia (fig. 9) both before and after the period of atrial pacing.
Localization of conduction delay in the A-V node during initiation of supraventricular tachycardia. Top trace—time marks every 100 msec; second trace—atrial electrogram (AEG) recorded from crista terminalis; third trace—nodal action potential; bottom trace—His bundle electrogram (HBE). Numbers represent atrial cycle lengths in msec. (Panels A, B, and C) Initiation of three successive atrial tachycardias at constant coupling interval between the sinus beat and premature atrial depolarization (indicated by arrow) (175 msec). Stimulus artifact is seen prior to the premature atrial impulse on the AEG recording. (Panel A) Microelectrode in the AN region. (Panel B) Microelectrode in the NH region. (Panel C) Microelectrode in the NH region. Increment in conduction of premature impulse through the total A-V node (change in atrial to His bundle electrogram interval) is confined mainly to the interval between atrial electrogram and AN cell (Panel A).

In contrast to the changes in the cells in the AN region of the node there were no major alterations in the configuration of action potentials recorded from middle (N region) or lower (NH region) nodal cells during tachycardia. Although a slight decrease in resting potential, total action potential amplitude, and duration were usually observed (figs. 1 and 10), no “humps” occurred. All changes in action potential characteristics of N and NH cells could be duplicated by pacing the atrium at a cycle length similar to the tachycardia.

During tachycardia, conduction through the A-V node to the His bundle exhibited various degrees of block ranging from 2:1 block to Wenckebach periodicity in only four instances (fig. 10). When this occurred, conduction was never blocked within the AN region of the node. During tachycardia, when an atrial impulse was not conducted to the His bundle, action potentials from N cells exhibited only a small local depolarization, indicating that conduction failed a short distance proximal to the recording electrode (fig. 10D). No depolarization of cells in the NH region of the node was seen during these blocked impulses (fig. 10F). During tachycardia, failure of conduction to the N or NH regions of the A-V node did not alter the atrial cycle length or effect the duration of tachycardia.

Tachycardia was always terminated by events occurring within the AN region of the A-V node. When the tachycardia was terminated by a stimulated premature atrial depolarization the impulse was conducted into the AN region of the node with prolonged conduction time (fig. 11). Premature atrial impulses terminating tachycardia did not have to penetrate the N or NH regions, but tachycardia was never terminated by a premature depolarization which failed to penetrate the upper A-V node.

Discussion

I. The Appropriateness of the Model

Recent studies have described the electrophysiologic characteristics of paroxysmal supraventricular tachycardia in the human heart in considerable detail. The appropriateness of our in vitro model of this arrhythmia can be assessed only by comparing the model to clinical supraventricular tachycardia (SVT).

In the following specifics our model tachycardia is identical to clinical SVT:

1. The tachycardia may be initiated by single stimulated atrial premature depolarizations only if they are evoked during a specific portion of the relative refractory

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Characteristics of upper nodal (AN) action potential during induced atrial tachycardia. Upper trace—atrial electrogram (AEG) near A-V node; middle trace—upper nodal action potential; bottom trace—His bundle electrogram (HBE). Numbers above the atrial electrogram indicate atrial cycle length in msec. Numbers above nodal potentials are the intervals between initial peak depolarization and peak of “hump” on repolarization limb in msec. Numbers below the HBE represent intervals between atrial and His bundle depolarization in msec. Time calibration above is 100 msec. Voltage calibration at left is 100 mv. (Panel A) First nodal action potential is initiated by a sinus impulse. A premature atrial depolarization (arrow) induces tachycardia. A “hump” appears on the repolarization limb of subsequent nodal action potentials. As the atrial cycle length increases, the “hump” appears later on the repolarization limb. This is not related to total A-V nodal conduction time which remained constant (100 msec). (Panel B) During tachycardia at a constant cycle length, the “hump” remains in a fixed position on the descending limb of the action potential. (Panel C) At termination of the tachycardia, the position of the “hump” again varies directly with atrial cycle length while total A-V nodal conduction time remains constant. The last atrial depolarization is conducted to the His bundle but does not reenter to excite the atrium again. Note there is no “hump” on the terminal nodal action potential.

(2) An echo zone could be established for each in vitro preparation, and the echo zone was related to A-V nodal conduction delay (figs. 5 and 6).

(3) The behavior of single and multiple reentrant beats closely paralleled the initiation of tachycardia, i.e., the first and second cycles of atrial echoes and tachycardia showed a reciprocal relationship (figs. 2 and 6).

(4) There was an initial oscillation of atrial cycle lengths during tachycardia which was inconsistent with pacemaker warm-up behavior (fig. 1).

(5) The initiation of tachycardia was unrelated to stimulation during the atrial vulnerable period (see below—Components of the Reentrant Pathway).

(6) Tachycardia could be terminated in every instance by an appropriately-timed single stimulated atrial premature depolarization (fig. 11).

There are two obvious differences between our model arrhythmia and clinically occurring SVT:

(1) Tachycardia never developed spontaneously in our model. However, the complete absence of premature atrial beats in the unstimulated preparation, and the total dependence upon stimulated atrial premature depolarizations to initiate tachycardia, argues strongly for the fact that the tachycardia is a reentrant arrhythmia.

(2) Whereas supraventricular tachycardia in the human heart has an atrial cycle length of 300–425 msec (150–200 beats/min), the cycle length of the model tachycardia was 180–216 msec (270–330 beats/min). This apparently significant difference, however, turns out to be another demonstration of the appropriateness of the
Figure 9

Effect of atrial tachycardia and rapid atrial stimulation on action potential configuration of cells in the AN nodal region. Time calibration above is 100 msec. Voltage calibration to the left is 50 mv. Remaining format is the same as figure 8. (Panel A) Basic cycle length and configuration of upper nodal action potential during sinus rhythm. (Panel B) Action potential configuration of the same cell as in panel A, during induced tachycardia (note “hump” on repolarization limb). 1:1 atrioventricular conduction occurs during the tachycardia. (Panel C) Basic cycle length and configuration of transmembrane action potential recorded from a different cell in the same region as panel A, immediately after termination of tachycardia. (Panels D and E) Rapid atrial pacing at cycle length identical to panel B. Note there is no “hump” on repolarization limb of this cell during pacing. Also, after 15 cycles, 3:1 atrioventricular block developed (E).

model. The rate of supraventricular tachycardia in the human heart has been shown to be a linear function of the refractory periods of the A-V node. In patients studied, A-V nodal functional refractory periods ranged from 340 to 450 msec and effective refractory periods from 240 to 340 msec. Patients with the most rapid SVT had the shortest A-V nodal functional and effective refractory periods. In our model, the refractory periods of the rabbit A-V node were much shorter than those of the human heart. Rabbit A-V nodal functional refractory periods ranged from 180 to 210 msec, and effective refractory periods from 115 to 148 msec. If the relationship between A-V nodal refractoriness and the cycle length of SVT determined in the studies of Bigger and Goldreyer in man is extrapolated to the refractory period values encountered in the rabbit A-V node, the expected atrial cycle length during model tachycardia would be 160–220 msec. The values for cycle length observed in our model closely correspond to those predicted by the human studies.

II. Conclusions from the Model

A. Components of the Reentrant Pathway

Since the tachycardia induced in the isolated rabbit right atrium is an appropriate model of its clinical counterpart, paroxysmal supraventricular tachycardia, it provides a suitable preparation to investigate the mechanism of this arrhythmia. The effects of sectioning various anatomical regions in the isolated right atrium provides direct evidence that the A-V node has an indispensable role in the initiation and maintenance of this arrhythmia.

Sectioning the His bundle or various regions of the atrium had no effect on our ability to produce tachycardia. Participation of the sinus node in the genesis of this arrhythmia is not excluded. Removal of a large part of this structure did not affect the tachycardia. This suggests that the presence of the sinus node is not critical although it still may be involved in the reentrant pathway. Atrial muscle must be part of the reentrant pathway since removal of
A-V nodal action potentials during three episodes of atrial tachycardia with failure of 1:1 atrio-ventricular conduction. The format is identical to figure 7. (Panels A and B) Upper nodal action potentials during sinus rhythm (A) and atrial tachycardia (B). Note that depolarization of this AN cell occurred following every atrial depolarization even when the atrial impulse failed to conduct to the His bundle. (Panels C and D) Middle nodal (N) action potential during sinus rhythm (C) and atrial tachycardia (D). N cell is not actively depolarized when the atrial impulse is not conducted to the His bundle, but exhibits a small local depolarization. Atrial cycle length is unaltered. (Panels E and F) Lower nodal (NH) action potential during sinus rhythm (E) and atrial tachycardia (F). NH cell shows no depolarization when an atrial impulse is not conducted to the His bundle. Despite this, the atrial cycle length during tachycardia remains steady at 190 msec.

Termination of atrial tachycardia with a premature atrial impulse. Top trace—atrial electrogram (AEG); middle trace—upper nodal action potential during tachycardia; bottom trace—His bundle electrogram (HBE). Time calibration above is 100 msec. Voltage calibration to the left is 100 mv. Numbers above the AEG represent atrial cycle lengths in msec. The cycle length of the tachycardia is 216 msec. A premature atrial depolarization (arrow) is induced during the tachycardia 166 msec after the previous atrial depolarization. The premature impulse penetrated the upper node but failed to reach the His bundle. The tachycardia was terminated. Note that the nodal action potential terminating the tachycardia failed to exhibit a “hump” on its descending limb.

A large mass of atrial tissue prevents the initiation of tachycardia. The indispensability of the functional intactness of the A-V node in the initiation of tachycardia was demonstrated when after a discrete lesion was placed at the border of the A-V node and atrium, tachycard-
dia could no longer be produced. The discreteness of this lesion and the specificity of its results excludes the possibility that tachycardia might be due to reentry elsewhere in the right atrium, i.e., in the atrial myocardium itself. It also eliminates the possibility that the tachycardia was due to atrial "vulnerability." These findings provide direct confirmation of the conclusions arrived at in studies of the human arrhythmia.9

B. The Site of Reentry

Microelectrode recordings from the A-V node provide further evidence that SVT is due to reentry and localizes the reentrant site to the upper A-V node. Tachycardia was induced in vitro by a premature atrial depolarization which showed marked conduction delay in the upper A-V node (AN region). Theoretically, reentry of the cardiac impulse can occur when conduction is slow enough to permit the recovery of excitability of tissue depolarized prior to or during the interval of conduction delay.14 It has been suggested that reentry in the upper A-V node occurs due to functional longitudinal dissociation of cells in this region.12, 15, 16 An early premature impulse finds certain cells excitable and others refractory when it enters the upper node. It therefore traverses the excitable tissue, during which time refractory tissue has recovered providing a return pathway to the atrium. Slow conduction in the upper node would allow time for atrial muscle to recover excitability and be activated during reentry. This sequence of events has been directly demonstrated by Mendez and Moe.12

Our recordings suggest that the upper node (AN and possibly part of the N region) is necessary for the genesis of supraventricular tachycardia. Conduction delay of the premature atrial depolarization inducing in vitro tachycardia occurred primarily in the AN region (fig. 7). Since conduction delay is a prerequisite of reentry, it is likely that reentry is occurring where conduction delay is maximal. Furthermore, although during tachycardia, impulses might block in the N and NH regions, the AN region of the node depolarized with every atrial cycle (fig. 10).

This, however, does not eliminate the possibility that reentry can occur in other regions of the A-V junction.

Action potentials recorded from cells near to or within a reentrant pathway may be expected to exhibit the configuration shown in our recordings from AN cells during tachycardia (figs. 8–11). The "humps" which occurred are probably due to electrotonic interaction between adjacent cells depolarized out of phase due to slow conduction, for similar electrotonic interactions have been noted during slow conduction in both the A-V node and Purkinje fibers.18, 17 The initial depolarization of the upper nodal cells probably occurs during passage of the atrial impulse into the A-V node. The "hump" on the repolarization limb of the action potential is most likely due to an adjacent upper nodal cell which is depolarized considerably later than the cell from which electrical activity is being recorded and, because of slow conduction, provides a possible return route to the atrium. The "hump" on the repolarization limb of the upper nodal cells is probably not due to a second active depolarization of the same cell since it occurs at a time when A-V nodal cells are still inexcitable.18, 19 The electrotonic depolarization "hump" seen during tachycardia was not related to antegrade conduction to the His bundle since its time of appearance was not related to changes in overall A-V conduction time (as has been demonstrated for instance in electrotonic interactions in the middle and lower node).18 The "hump" is similarly not a result of adjacent atrial depolarization since it occurred before the reentrant atrial activation. The time at which the "hump" occurred, however, did vary with the atrial cycle length during tachycardia indicating a relationship to the reentrant pathway. When conduction was prolonged through the reentrant pathway resulting in a long atrial cycle length, the "hump" occurred later in repolarization of the A-V nodal cell. This would be expected if the "hump" is due to electrotonic interaction between cells in the reentrant pathway, since during a long atrial cycle length, conduction through the reentrant pathway.
pathway is slower, and, therefore, adjacent cells would be depolarized later in time. In addition, the "hump" never appeared after the last atrial depolarization of tachycardia which, although conducted to the His bundle, was not conducted back to the atrium (fig. 8).

C. An Evoked Pacemaker?

It has been suggested that premature depolarization of the A-V node can excite a junctional pacemaker to fire spontaneously at a rapid rate, and that this is the mechanism of SVT.4 Our model refutes this hypothesis. If the premature atrial impulse did excite a pacemaker in the A-V nodal region, the tachycardia should be demonstrable even after the removal of large masses of atrial muscle (i.e., as long as the premature impulse still had access to the A-V node). This did not occur. The possibility also exists that the premature impulse somehow excites an ectopic pacemaker in the specialized atrial fibers. However, if this were so, the prevention of the tachycardia by a discrete A-V nodal lesion could not be explained. In addition, premature atrial impulses which penetrated into the upper A-V node did terminate the tachycardia. This would be expected only if the node were part of a reentrant pathway.

D. Significance of the Model

The in vitro replication of clinically occurring cardiac arrhythmias has considerable potential significance. The induced in vitro tachycardia reported here is an appropriate model since it is identical in every way to paroxysmal supraventricular tachycardia in man. The model extends our understanding of the mechanism of that arrhythmia by the application of recording techniques which cannot be utilized in the clinical setting. In addition to documenting the mechanism of SVT it should provide a convenient tool for the study of the efficacy of antiarrhythmic drugs.

References


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