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Impulse propagation from the SA-node to the ventricles

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Summary. Normally the pacemaker of the mammalian heart is located in the sinus node. In the rabbit the sinus node can be subdivided into two regions, the center of the node where the impulse originates and the border zone through which the impulse is conducted towards the atrium. Conduction properties of both regions were investigated. It appeared that conduction velocity increases and refractoriness decreases when one goes from the nodal center towards the atrium. The tissue mass of the atrium is large in comparison to the sinus node and normally the resting membrane potential of atrial fibers is more negative than that of nodal fibers; consequently, a potential difference exists causing a current flow between both areas. Evidently this hyperpolarizing current flow depresses impulse formation in the border zone fibers which have better intrinsic pacemaker properties than fibers in the nodal center. If the impulse has reached the atrium it is conducted with a relatively high safety factor and will reach the AV node in principle without difficulty. The AV node, if deprived of sinus nodal dominance, develops spontaneous activity originating from the lower nodal fibers. Also in this structure, electrotonic depression by surrounding tissue causes deceleration of the pacemaker.
Key words. Sinus node; nodal impulse conduction; AV node; impulse formation; electrotonic influence.

Introduction

The electrical impulse which initiates every beat of the mammalian heart normally originates from the sinus node. Although impulse formation represents only a small part of the electrical events in the heart, different electrophysiological disturbances can occur which influence sinus nodal functioning[6, 11].

The isolated rabbit sinus node has been investigated widely and has yielded a lot of knowledge about this structure. Within the rabbit sinus node two distinct regions can be distinguished: the compact zone or nodal center and the periphery or nodal border zone[3, 16]. Normally the site of impulse origin is found in the center of the isolated sinus node[3]. The action potentials recorded from these fibers have typical characteristics of automaticity. The fibers which generate the earliest action potential within a heart cycle are indicated as the pacemaker of the sinus node and thus of the heart. It is probable that the impulse does not originate in one particular fiber but in a group of fibers depolarizing simultaneously and located somewhere in the nodal center. However, since this impulse should activate the atrial myocardium and the rest of the heart, it has to be conducted from its site of origin through the nodal center and border zone towards the atrium (crista terminalis).

Impulse conduction in the rabbit sinus node

From earlier studies it is known that intra-nodal impulse conduction is slow and deterioration can lead to sinus nodal dysfunction[9, 17]. We investigated conduction properties in the border zone as well as in the center of the isolated rabbit sinus node.

The preparation used included the roof of the right atrium, the crista terminalis and the intercaval tissue in which the sinus node is embedded. An incision was made, perpendicu-

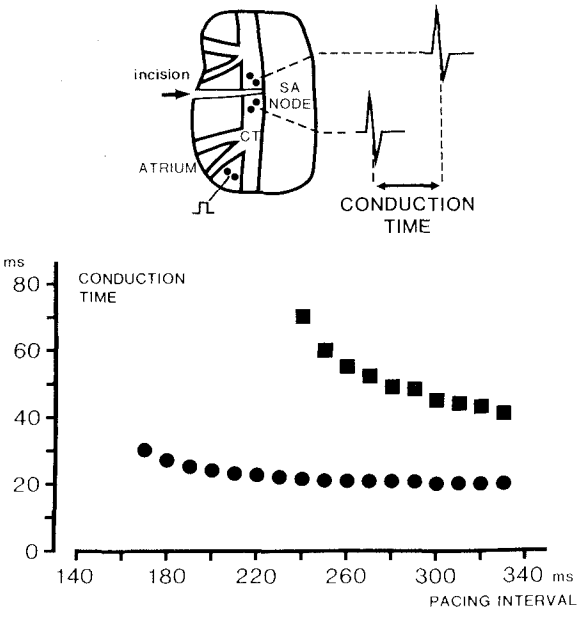

Figure 1. Upper part: schematic representation of the isolated sinus node preparation and the incision made to investigate conduction properties within the sinus node. The black dots represent bipolar surface electrodes placed near the entrance and exit of the nodal tissue bridge. Conduction time was determined by calculation of the time difference between the registered complexes. Lower part: diagram depicting the conduction time (ms) at decreasing pacing intervals both in the border zone and in the center of the sinus node. Conduction through the nodal center is slower and the maximal pacing interval markedly longer than in the border zone. Note that the rate-dependent increase of conduction time occurs in the center at longer intervals than in the border zone. CT = crista terminalis.

lar to the crista terminalis, dividing the atrium into two halves. In the upper part of figure 1 a schematic representation of the preparation is given. When the incision was continued through the crista terminalis just into the sinus node a preparation was obtained in which the two atrial halves were only connected by a bridge of nodal tissue. Two bipolar surface electrodes (Teflon-coated silver wire) were positioned on both parts of the crista terminalis, as close as possible to the incision and the sinus node. In this set-up an impulse evoked in one of the atrial halves via a stimulating electrode could activate the other atrial half only when conducted through the sinus nodal tissue bridge. The conduction time through this tissue bridge was measured by calculation of the time difference between the activation complexes registered by the electrodes at the 'entrance' and 'exit' of the tissue bridge (fig. 1). This conduction time was calculated during different stimulation protocols. From preliminary experiments it appeared that an impulse evoked in one atrial half always traveled along the shortest route around the tip of the incision towards the other atrial half. Therefore the length of an incision into the sinus node determined the region of the node investigated. In order to study conduction properties within the sino-atrial border zone an incision just through the crista terminalis was made. Continuation of this incision into the sinus node by 600 µm (measured from the transition between crista terminalis and border zone which was determined by means of microelectrode impalements) produced a preparation in which the impulse had to travel through the nodal center.

The diagram in the lower part of figure 1 depicts the conduction time at different pacing intervals in case of conduction through the border zone (circles) and through the center of the sinus node (squares). While pacing with 3 Hz, a frequency only slightly higher than sinus rhythm, conduction time through the border zone was 20 ms. When the pacing interval was shortened conduction time increased slightly but gradually to 28 ms at a pacing interval of 170 ms. This was the shortest pacing interval during which all impulses were conducted through the tissue bridge. In the center of the sinus node conduction was markedly slower. During pacing with 3 Hz conduction time was 43 ms. While the pacing interval was shortened, conduction time began to increase immediately and in an exponential way when approaching the shortest pacing interval which could be conducted in a 1:1 manner. In this case the shortest pacing interval was 240 ms and conduction time 90 ms. This example makes obvious that conduction through the center of the sinus node is much slower than through the sino-atrial border zone whereas Wenckebach conduction occurs in the center at far lower pacing frequencies than in the border zone. In the case of an incision into the center of the sinus node, the measured conduction time is a combination of impulse conduction through the border zone and through the center of the node. However, the increase in conduction time in the nodal center takes place at pacing intervals at which almost no increase is found in the border zone. Therefore the rate-dependent increase of conduction time in the case of an incision into the nodal center is not due to a simultaneous deceleration of conduction in the border zone. While pacing with 3 Hz premature stimuli were applied as well. When the interval between the test stimulus and the previous basic stimulus was shortened conduction time increased both in the border zone and in the center of the node. The shapes of both curves were identical to the ones described above during shortening of the pacing interval. The only difference was that one single premature impulse could be conducted through the border zone or nodal center with more prematurity than a train of stimuli. Thus both curves were shifted to the left in the diagram. From these studies it appeared that conduction in the isolated rabbit sinus node is much slower than in the atrium and that conduction velocity decreases and refractory period increases drastically on going from the border zone towards the center of the sinus node. From a series of experiments we obtained the data given in the table. From these data and the carefully measured length of the conduction pathway we were able to calculate the mean conduction velocity in the border zone and in the nodal center: 9 and 3.5 cm/s, respectively.

Influence of the atrium on nodal impulse formation

An impulse generated in the sinus node and conducted through the border zone reaches the crista terminalis and will finally activate the whole atrium. The crista terminalis is many times thicker than the connected sinus node. Furthermore the atrial fibers have a more negative membrane potential in comparison to the sinus nodal fibers during the electrical diastole[3, 16]. Therefore we investigated whether the crista terminalis has any influence on sinus function. In order to answer this question the atrium was disconnected from the sinus node by making an incision along the transition of crista terminalis and sinus node by means of a fine pair of scissors. Before this procedure the sinus node was investigated under control conditions. Sinus rhythm was monitored and beat to beat interval calculated continuously. Multiple intracellular recordings were performed by means of stan-

	Border zone n = 41	Center n = 39
Conduction time pacing 3 Hz (ms)	17 ± 6	42 ± 24
Minimal pacing interval (ms)	165 ± 25	240 ± 38
Effective refractory period (ms)	110 ± 16	165 ± 29

All values represent mean ± SD.

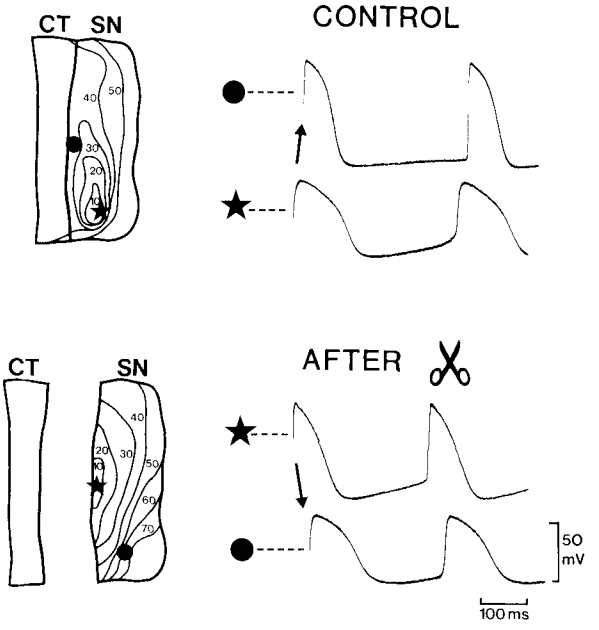

Figure 2. Upper part: activation pattern (left) of the sinus node under control conditions, visualized by means of isochrones (10 ms), and examples of action potentials (right) recorded in the border zone and center of the node. The black star represents the site of the pacemaker. Lower part: activation pattern of the sinus node after disconnection from the atrium (represented by a pair of scissors) and examples of action potentials recorded in the same site as under control conditions (upper part). The pacemaker is shifted to the border zone accompanied by an increase in diastolic depolarization rate of the action potential from this area. Note the reversed time relation (arrows) of the action potentials under control conditions and after disconnection of atrium and sinus node. See text for further explanation. CT = crista terminalis; SN = sinus node.

dard microelectrode techniques to determine the site of impulse formation (earliest activation) and nodal activation pattern. Under normal conditions beat to beat interval in 15 experiments was 348 ± 50 ms (mean ± SD). In the left upper part of figure 2 the activation pattern of the sinus node of one (representive) experiment is depicted. The pacemaker (black star) was found at about 1 mm from the crista terminalis obviously within the center of the sinus node. The activation pattern of the node is visualized by means of isochrones (10 ms). From its site of origin the impulse is first conducted relatively slowly through the nodal center but accelerates in the nodal border zone and activates the atrium after 20 ms. Considering earlier studies[3,4,12,14] this is a normal activation pattern. At the right typical action potentials are given, recorded in the nodal center at the location of the pacemaker and in the nodal border zone. The action potential in the center of the node shows a slow upstroke, a long duration, a low amplitude, a low maximal diastolic potential and a high rate of diastolic depolarization. The action potential recorded in the border zone on the other hand has a steeper upstroke, a shorter duration, a larger amplitude, a more negative maximal diastolic potential and a slow rate of diastolic depolarization. Furthermore, a time latency to the action potential of the fiber in the nodal center exists.

After these control measurements had been performed the atrium was disconnected from the sinus node; then sinus rhythm accelerated during the next 20–30 min. Thereafter the rhythm became stable and did not alter any more during the further course of the experiment. One hour after stabilization the mean beat to beat interval was 288 ± 42 ms, which is a significant shortening of 17% with respect to the control situation. Determination of the pacemaker location and subsequent activation pattern revealed that the observed rhythm acceleration was accompanied by a shift of the pacemaker from its previous site in the nodal center towards a new location in the border zone of the sinus node. This is depicted in the lower part of figure 2. In this case the pacemaker, represented by the black star, is located in the border zone. The activation pattern is changed consequently. The impulse is conducted in a reversed direction, from the border zone into the nodal center. The clue to this pacemaker shift becomes clear after considering the action potentials, given at the right of the activation map (lower right side of fig. 2). These recordings are obtained from the same sites as the ones during control conditions. When comparing the action potential from the border zone, at the site of the pacemaker, with the one under control conditions, it can be seen that the rate of diastolic depolarization has increased enormously. But this is not the case in the nodal center. Comparing these action potentials reveals that in the center, diastolic depolarization rate is not increased but is even slightly decreased. The transition to the upstroke of the action potential has become much smoother in the border zone whereas in the center of the node this property has disappeared. Thus after disconnection of atrium and sinus node there is an increase in diastolic depolarization rate in the fibers of the border zone accompanied by a shift of the pacemaker. In the other experiments the same qualitative results were obtained; there was no preferential site for the location of the pacemaker in the border zone.

Since the observed increase in the rate of diastolic depolarization was not found in the center of the sinus node we investigated the relation between the distance from the atrium and changes in diastolic depolarization rate due to disconnection of the atrium. Therefore a series of impalements arranged in a line perpendicular to the crista terminalis was made. The findings of one of these experiments are given in the diagrams of figure 3. The upper diagram depicts the control situation. In the border zone, represented by impalements at 100, 300 and 500 μm from the crista terminalis, rate of diastolic depolarization is 20, 30 and 35 mV/s,

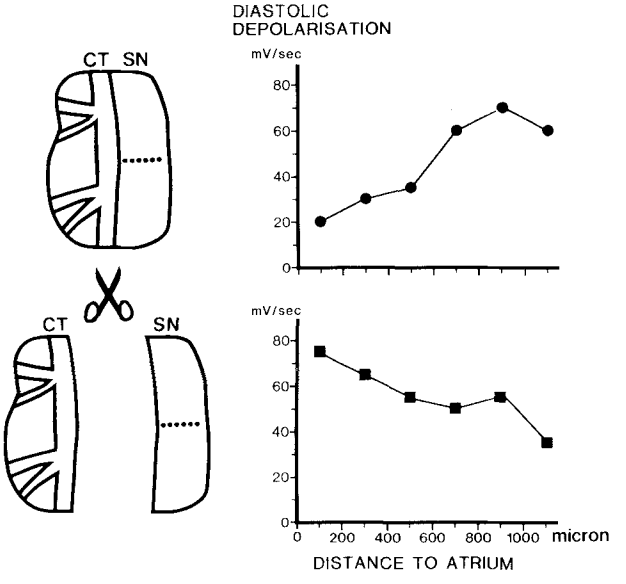

Figure 3. Diastolic depolarization rate (mV/s) at increasing distance from the atrium. In the upper diagram it can be seen that under control conditions diastolic depolarization rate is low in the border zone but increases when going towards the center (increasing distance). This relation is reversed after disconnection of atrium and sinus node. Then the maximal rate is found in the border zone and decreases slightly towards the nodal center. CT = crista terminalis; SN = sinus node.

respectively. Although a tendency towards increase is present, these values are low in comparison to the values obtained in the center of the node. Here, at 700, 900 and 1100 µm distances from the crista terminalis, diastolic depolarization rate was 60, 70 and 60 mV/s. A distance of 900 µm from the crista terminalis corresponded to the region in the sinus node were the pacemaker was found. However, after disconnection of atrium and sinus node the observed relation between diastolic depolarization rate and distance from the crista was reversed (lower diagram). In the border zone at 100 µm from the sino-atrial transition rate of diastolic depolarization was 75 mV/s. At increasing distances diastolic depolarization rate in the border zone decreased slightly to 65 and 55 mV/s at 300 and 500 µm respectively, whereas this tendency continued in the nodal center. At distances of 700, 900 and 1100 µm diastolic depolarization rates of 50, 55 and 35 mV/s respectively were found. In different experiments the same qualitative results were obtained. Obviously disconnection of the atrium causes an increase of the rate of diastolic depolarization of fibers in the border zone which is maximal close to the sino-atrial transition. In the nodal center this increase was not observed and even a decrease was found. Consequently a pacemaker shift occurs. The increase in diastolic depolarization rate combined with the given shorter action potential duration of the border zone fibers explains the acceleration of sinus rhythm.

How can the described findings be explained? Injury occurring during the disconnection procedure of atrium and sinus node might be the reason for the observed events. However, this is very unlikely since the rate acceleration became stable and persisted during the further course of the experiment, lasting at least 3 h. If injured fibers were the origin of the acceleration one would expect this to last until these damaged fibers were healed-over or definitely dead. This process lasts only 10–30 min[2, 5, 7, 8] and therefore can not explain the long-term rhythm acceleration. Another argument against a role of injury is that no dramatic changes in action potential configuration were found in the border zone fibers. The maximal diastolic potential in 73 impaled fibers was −61 mV before and −62 mV after disconnection of atrium and sinus node. In case of injury, depolarization might be expected. Another, more reasonable explanation for the observed events is an electrotonic depressive influence of the atrium on the fibers in the border zone. The fibers in the atrium have a more negative resting potential than fibers in the border zone of the sinus node. Consequently during the electrical diastole a potential difference exists between the two fiber types which causes a passive current flow hyperpolarizing the border zone fibers and depolarizing the atrial fibers. This phenomenon is complicated by the diastolic depolarization of the border zone fibers, since this increases the potential difference in the further course of the electrical diastole and thus the amount of current flow between the two fiber types. The hyperpolarizing current flow will decrease the rate of diastolic depolarization in the border zone fibers continuously but has no, or only limited, influence on more distal fibers in the center of the node. The slight decrease in diastolic depolarization rate as observed in the nodal center after disconnection of the atrium (fig. 3) is due to overdrive suppression caused by the accelerated sinus rhythm. Since the capacitance of the crista terminalis is enormous the depolarizing effect of the passive current flow on the atrial fibers is undetectable.

From these findings it was concluded that the rate of diastolic depolarization in fibers of the border zone is electrotonically depressed by the connected atrium and that the intrinsic pacemaker rate of these fibers is higher than in the nodal center. Furthermore, since this electrotonic influence of the atrium is based on intercellular electrical coupling, disturbances with respect to this might lead to sinus arrhythmias.

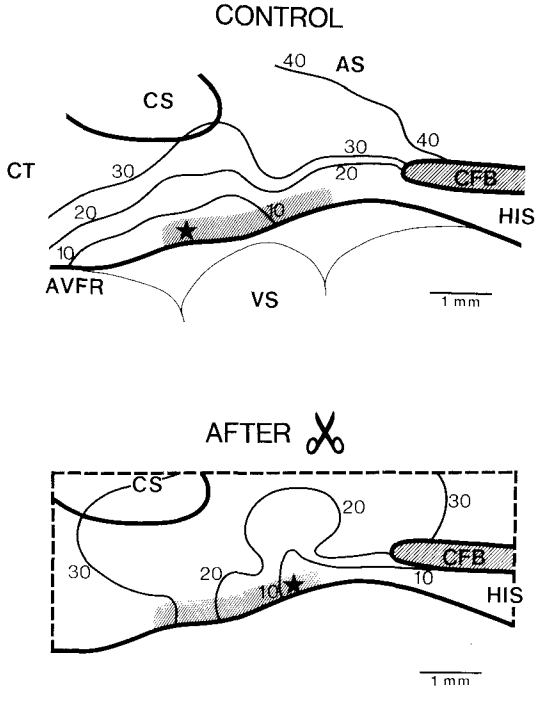

Figure 4. Activation pattern of the spontaneously active AV node under control conditions (upper part) and after isolation (represented by a pair of scissors) from the surrounding tissue (lower part) visualized by means of isochrones (10 ms). The location of the pacemaker is indicated by the black star. The shaded area represents the region in which the pacemaker was found in all experiments. CT = crista terminalis; CS = coronary sinus; AS = atrial septum; CFB = central fibrous body; His = proximal His-bundle; VS = ventricular septum; AVFR = atrioventricular fibrous ring.

Electrotonic influence on impulse formation in the AV node

When the crista terminalis is activated the impulse will spread over the atrium rapidly and will reach the AV node in which it is delayed and finally transmitted into the His-bundle. However, the junctional region of the mammalian heart is also capable of impulse formation as is known from many experimental and clinical investigations[13, 15, 18–21]. We investigated impulse formation in the junctional region of the rabbit heart and studied the presence of electrotonic interactions. The preparation described earlier by Paes de Carvalho et al.[10] was used. Under control conditions and after elimination of the sinus node the junctional preparation was spontaneously active. The mean spontaneous interval in 15 preparations was 1001 ± 311 ms (mean ± SD). This rhythm remained stable except for a slight increase of the interval by about 1 ms per min. Multiple impalements were performed to determine the location of the pacemaker (earliest activation) and activation pattern of the junctional region. The upper part of figure 4 depicts the activation pattern of one of the preparations under control conditions. Location of the pacemaker is indicated by a black star. The activation sequence is visualized by means of isochrones (10 ms). The pacemaker is located near the atrio-ventricular fibrous ring (AVFR) and within the AV node itself regarding the anatomical landmarks. From this site the impulse is conducted rapidly in antegrade direction towards the His-bundle but relatively slowly in retrograde direction towards the atrium. The shaded area represents the resultant region in which the pacemaker was found in all experiments (n = 15). By mapping the AV nodal activation sequence of a normal sinus beat

it was found that the region of maximal conduction delay within the AV node was located proximal to the above mentioned 'pacemaker-region'.

From these findings combined with the typical action potential characteristics and the rapid conduction of the impulse towards the His-bundle we concluded that under normal conditions but after failure of the sinus impulse the junctional pacemaker is located in the NH-region[10] or Lower Nodal Fibers[1] of the rabbit AV node. In order to investigate whether this impulse formation is also depressed electrotonically by surrounding tissue we tried to isolate the AV node. This was done by disconnection of the atrial myocardium at the side of the crista terminalis, coronary sinus and atrial septum, and by disconnection of the upper tissue sheet including the AV node from the underlying tissue mass. At the distal side of the AV node the His-bundle and surrounding tissue was removed. After this procedure the isolated AV node remained spontaneously active. However, the rhythm was accelerated markedly. The mean beat to beat interval was decreased from 1001 ± 311 ms under control conditions to 439 ± 111 ms after isolation and stabilization of the rhythm. The lower part of figure 4 depicts the activation pattern and pacemaker location after isolation of the AV node: the pacemaker is shifted over a certain distance in the direction of the His-bundle but is still located within the shaded 'pacemaker-region'. The latter was the case in all isolated AV node preparations, whereas an actual shift of the pacemaker within this region was found only in half of the experiments. In the example depicted in figure 4 conduction velocity of the impulse was still relatively high in the direction of the site where the His-bundle was located, whereas in the other direction, towards the atrium, an initial conduction delay was found, followed by more rapid conduction in the proximal AV node. Similar activation patterns were found in other experiments.

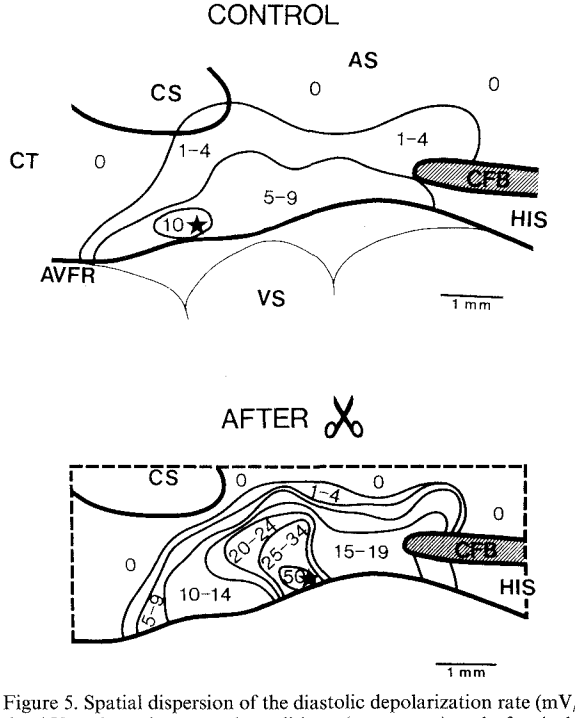

Figure 5. Spatial dispersion of the diastolic depolarization rate (mV/s) in the AV node under control conditions (upper part) and after isolation from the surrounding tissue (lower part). Under control conditions the maximum was 10 mV/s, found at the location of the pacemaker (black star), and became 50 mV/s at the location of the pacemaker after isolation of the AV node. For abbreviations see legend figure 4.

Is an increase in diastolic depolarization rate also responsible for the observed rhythm acceleration in the AV node? In figure 5 the spatial dispersion of diastolic depolarization rate under control conditions and after isolation of the AV node is given. Under control conditions (upper part of the figure) the highest rate of diastolic depolarization was 10 mV/s and was found within the region of Lower Nodal Fibers corresponding to the location of the pacemaker (note that the maximum is much lower than in the sinus node). The situation after isolation of the AV node is given in the lower part of the figure. Now the highest rate of diastolic depolarization was 50 mV/s, found at the same site. The increase in diastolic depolarization rate explains the rhythm acceleration seen after isolation of the AV node. These results suggest that a depressive influence of surrounding tissue on impulse formation is also present in the AV node. However, this increase in diastolic depolarization rate was not observed at the atrial side of the preparation. This might be caused by the fact that the transition between the atrium and the AV node (AN-region) is not sharp and therefore isolation at this side of the preparation probably failed because part of the atrium was still in situ and depressing diastolic depolarization rate at this side of the AV node. This means that removal of electrotonic influence of the His-bundle fibers and of tissue underneath the Lower Nodal Fibers is responsible for the increased diastolic depolarization rate found in the latter fibers. From these results it was concluded that impulse formation in the rabbit AV junction takes place in the NH-region or Lower Nodal Fibers of the AV node and that this pacemaker activity is electrotonically depressed by the connected His-bundle and underlying tissue.

General conclusions

Sinus node functioning is based on impulse formation and impulse conduction. In the isolated rabbit sinus node the pacemaker is normally found in the nodal center. It appeared that fibers in the border zone of the sinus node have better intrinsic pacemaker properties than the fibers in the nodal center. However, the former are electrotonically depressed by the connecting atrium. From the site of pacemaking the impulse has to be conducted through the nodal center and nodal border zone towards the crista terminalis. It was found that impulse conduction in the nodal center is very slow, namely 2–5 cm/s, and the refractory period very long, namely 165 ms. In the border zone impulse conduction is faster than in the nodal center, namely 7–11 cm/s, whereas the refractory period is remarkably shorter, namely 110 ms. After activation of the atrium the impulse reaches the AV node. Although this structure normally functions as a slow conducting pathway it exhibits pacemaker properties under certain conditions. In that case the impulse originates from the lower nodal fibers. The rate of AV nodal impulse formation is much lower than the normal sinus rate. However, it appeared that also in the rabbit AV node impulse formation is depressed electrotonically by the surrounding myocardium, since after isolation of the proper AV node the spontaneous AV rhythm accelerated remarkably.

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Mechanisms for cardiac arrhythmias

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Summary. Possible cellular electrophysiological mechanisms for arrhythmias have been investigated through studies of isolated cardiac tissues. Records through extracellular and intracellular electrodes indicate that arrhythmias may result from either focal or non-focal mechanisms. Focal mechanisms include abnormal impulse initiation (normal or abnormal automaticity,), triggering from either early or delayed afterdepolarizations and reflection, whereas the non-focal mechanisms are various forms of reentry due to circus movement. It is reasonable to assume that these mechanisms also occur in vivo. Although it is safe to identify macro-re-entry as the cause of some atrial and ventricular arrhythmias, for the most part direct proof of mechanism usually is lacking for the focal arrhythmias. If 'on line' activation sequence mapping techniques can be developed to quickly and specifically locate arrhythmogenic foci in the in situ heart, it may be possible to use unipolar extracellular recording techniques to identify the exact cellular electrophysiological mechanisms operating within them.
Key words. Cardiac arrhythmias; reentry; triggering; automaticity; transmembrane action potentials; early afterdepolarizations; delayed afterdepolarizing actions.

Mechanisms for cardiac arrhythmias

A consideration of the mechanisms for cardiac arrhythmias must deal with two different types of questions. First, it is necessary to identify the abnormalities of cellular electrical function or structure that can induce arrhythmic activity. These abnormalities may be induced by either pathological processes or by experimental interventions. Second, it then is necessary to determine which of these possible mechanisms are actually responsible for specific arrhythmias in the in situ heart. The problem in this case is to be able to make a certain and explicit identification of the cellular electrophysiological mechanism that is involved in the genesis of the rhythm disturbance. It is possible that the response of many arrhythmias to therapeutic interventions depends on the mechanism causing the arrhythmia. Even though the evidence for this presumed dependence is not strong, the assumption deserves continuing tests as improved drug design can provide agents with more restricted and specific activities. Furthermore, increasing our understanding of the mechanisms responsible for particular arrhythmias is important, because this knowledge should ultimately lead to improved drug therapy of cardiac disease and reduced morbidity and mortality.

Possible mechanisms

It is well established that certain normal cardiac cells have the property of automaticity. These cells include the pacemaker cells of the sinus node, as well as subsidiary specialized atrial fibers [26], the NH region of the atrioventricular junction[24], and the His bundle and Purkinje fiber ramifications in the ventricle[14]. It is reasonable to assume that, just as the activity of the sinus node pacemakers gives rise to normal or abnormal sinus rhythm, spontaneous impulse initiation in the subsidiary pacemakers can give rise to abnormal atrial or ventricular rhythms. Such abnormal rhythms might be manifest either as premature depolarizations or sustained rhythms that compete with or supercede the sinus rhythm. During sinus rhythm, the propagation of the cardiac impulse is an orderly process. The speed and direction of the impulse spread is controlled by the electrical properties and spatial distribution of the cardiac fibers. As a result of this and the long duration of the refractoriness of cardiac cells, when a sinus impulse has activated the tissues excited last in the normal activation sequence, all of the adjacent tissues are refractory and propagation ceases. However, this need not be the case. A localized unidirectional failure of conduction,