CARDIAC PACING

Diagnostic and Therapeutic Tools

Edited by B. Lüderitz

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With 75 Figures

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Introduction

The history of electric cardiac stimulation is long and fascinating. The growing clinical importance has been recognized and renewed as Zoll in 1952 described a successful resusciation in cardiac standstill by external stimulation. Meanwhile, patients with disorders of cardiac rhythm have been treated all over the world for about 15 years. Recently the technical refinements of intracardiac stimulation in combination with a subtile analysis of endocavitary electrocardiograms improved the understanding of human intracardiac conduction. These new procedures include the possibility to study the initiation and termination of tachycardias. – The pertinent interest in these developments and the intention to learn more about the basic fundamentals of excitability and conduction under both normal and pathological circumstances were reasons to organize an international symposium on that topic. – The papers contained in this book were presented at this meeting on diagnostic and therapeutical tools of cardiac pacing, held at Munich on November 7 and 8, 1975, sponsored by the first Medical Clinic of the University of Munich and generously supported by Medtronic. Especially focused are the investigations on sinus node function, disturbances of av-conduction and electrophysiology of supraventricular and ventricular tachycardias. The content of the book that is emerging from the symposium were created by the authors. I wish to thank them for teaching us about the recent advances in cardiac tissue stimulation by electricity. Much credit is due Priv. Doz. Dr. B. Lüderitz, who organized the symposium and published these proceedings. I am sure that this meeting has contributed to the progress in understanding cardiac arrhythmias. I do hope that the advances in the field of diagnostic and therapeutic application of cardiac pacing will continue as rapid as before in order to give us further great help in taking care of the patient.

G. Riecker

I. Sinus Node

The Sinoatrial Node Function

F. I. M. BONKE

The impulse for the activation of the heart is generated normally in the sinoatrial node (SA node). This structure covers an area of only a few square millimeters. The cells have an irregular contour and are small (diameter less than 10 μ). Furthermore, they contain sparse myofilaments which are often not well organized. The intercellular junctions are different from normal myocardium since there are no intercalated discs, no real nexus, and only rare membrane junctions. The nodal cells often form clusters divided by connective tissue. One of the characteristic features of the SA nodal structure is the abundant innervation by autonomic fibers [15]. Since West [28] made the first impalement with a microelectrode in a fiber of a mammalian SA node, many researchers have studied the electrophysiologic characteristics of the node. Most of these studies were done with the rabbit heart. Although only little information about the human SA node is available, it seems reasonable to assume that there is no principal difference between man and rabbit in respect to the electrophysiology of the SA node.

Electrophysiology of the SA Node

The fibers of the SA node show a slow depolarization during diastole (phase 4 depolarization, prepotential) and, therefore, never have a real resting potential. Compared to atrial fibers, the maximal polarization of the membrane of the nodal fibers is less, the action potential has a lower amplitude and a longer duration, and depolarization is relatively slow.

However, the prepotential is not the same in all fibers of the node. In most of the fibers there is an abrupt transition from the prepotential into the depolarization phase of the action potential. It is clear that these fibers are brought to a discharge and are not generating a discharge themselves. If the prepotential was not interrupted these fibers would come to a spontaneous discharge. Therefore, they are called latent pacemaker fibers.

Any group of fibers in the SA node simultaneously coming to a spontaneous discharge, might act as the pacemaker of the heart. These fibers show a prominent prepotential (15 – 25 mV) and a smooth transition from prepotential to upstroke of the action potential. However, not all the fibers in the SA node in which these two conditions are fulfilled are dominant pacemaker fibers.

Only if the discharge of these fibers is conducted through the node to the atrium and serves as the impulse for the atrial activation, is it correct to call

these fibers dominant pacemaker fibers. In the rabbit, therefore, the latency between the depolarization of such a fiber and the activation of atrial fibers just near the nodal region (crista terminalis) has to be at least 30 – 35 ms. Since impulse conduction is very slow in the SA node — 0.1 – 5 cm/s — it is possible that more groups of fibers come to a discharge more or less simultaneously without affecting each other. Only the group of which the impulse reaches the atrial border first will be the pacemaker. Normally this dominant pacemaker is located in the center of the SA node. The impulse is conducted through the node discharging the surrounding nodal fibers. The fibers that are located more at the periphery of the node will be discharged either by another group of spontaneously discharging fibers or by an impulse invading retrogradely the SA node from the crista terminalis.

The slow conduction velocity in the SA node is correlated with the relatively slow upstroke velocity of the action potential and the relatively bad electrotronic interactions [3]. The result is that the fibers in the SA node can work asynchronously. The advantage is that the function of pacemaker can be taken over by another group of fibers for a shorter or longer period. Therefore, the shape of the action potential is changeable and the pacemaker can shift through the node from place to place. This will, for instance, occur when the temperature in or surrounding the SA node is changed. A decrease in temperature is coupled with a lowering of the prepotential and consequently with a decrease in heart rate. The effect of a temperature change is more pronounced in fibers with a prominent prepotential than in typical latent pacemaker fibers. The prepotential in the dominant pacemaker fibers is more depressed than in other fibers and hence a shift of the pacemaker takes place [8]. When the vagal tone is increased, the slope of the prepotential is diminished and with further increase of the vagal tone, hyperpolarization might occur or even a complete arrest of impulse generation. In these cases a shift of the pacemaker is obvious as demonstrated by Toda and West [27] and Bouman et al. [7]. Hence, the acetylcholine, liberated at the ending of the vagal nerve, has a stronger effect on the dominant pacemaker fibers than on the latent fibers. One might assume that the pacemaker shift is caused by an unequal distribution of the acetylcholine through the node, but a pacemaker shift occurs also when acetylcholine is added to the fluid surrounding the SA node (e.g., isolated right atrium preparation).

On the other hand, stimulation of the sympathetic nerves or addition of adrenaline to the perfusion fluid in the isolated right atrium preparation is attended with an increase in heart rate based on a faster slope of the prepotential. The site of the pacemaker in the SA node is influenced by the above-mentioned maneuvers as demonstrated by Toda and Shimanoto [26] and Lu and Brooks [18]. Moderate changes in the sodium or potassium concentration of the extracellular fluid have little influence on the slope of the prepotential. However, changes in the calcium concentration have a striking effect. An increase in calcium concentration is attended with an increased slope of the prepotential and consequently an increased heart rate. [23]. Whether the extracellular calcium concentration has an influence on the site of the pacemaker has to be investigated.

As we have now seen, practically all factors influencing the SA nodal fibers influence both the rate of discharge of the pacemaker and the site of this pacemaker within the SA node.

A more basic problem in the electrophysiology of the SA node is the question of the mechanism that underlies the prepotential. Since the SA nodal fibers are difficult to impale with microelectrodes because of their small size and the close vicinity of the contracting atrial myocardium, most investigators used the Purkinje fiber preparation to study this problem. Besides, direct measurement of current flow in sinoatrial node cells is practically impossible because of the structural complexity of the nodal tissue. So far as I know only Irisawa [13] has tried to use a double sucrose gap technique for voltage clamping of SA nodal tissue of the rabbit. His results are, however, preliminary and many problems have to be solved. The Purkinje fiber preparation is of all cardiac preparations the most suitable for current analysis by means of the voltage clamp technique [14].

Customarily the same explanation for the formation of the action potential and for the development of the prepotential in both Purkinje fiber and sinoatrial node is used. It turns out, however, that this generalization is not absolutely valid since there are too many differences in behavior and in sensitivity to changes in the environment between both types of fibers. I will not go into more details here, but would refer the reader to the recent monograph of Brooks and Lu [9].

I would like to put forward here the following hypothesis about the sinoatrial nodal fiber:

The SA nodal fibers are in principle normal myocardial fibers the cell membrane of which has an abnormally high permeability for ions. Therefore, these nodal fibers will contain more sodium and less potassium than cardiac fibers normally do. The most leaky fibers will be the dominant pacemaker.

Because of the complex geometry of the SA node, chemical analysis of the ion contents of these cells is very difficult. Mazel and Holland [20] found that the sinus venosus fibers of frog and turtle contained obviously more sodium and less potassium than atrial and ventricular fibers. This is the only direct support for my hypothesis at this writing. However, the following observations can be explained with this hypothesis:

1. The nodal fibers are the least polarized cardiac fibers.
2. The ratio between potassium permeability and sodium permeability will be relatively low and the nodal fibers, therefore, are not very sensitive for changes in extracellular potassium concentration.
3. Since the nodal fibers are partly depolarized the sodium transport system will be more or less inactivated and in combination with the relatively small difference between the intra- and extracellular sodium concentration, this can explain the fact that sodium ions are far less important as current carriers during the upstroke of the action potential than is the case in other cardiac fibers. (Nodal fibers are TTX-insensitive, but can perhaps be made sensitive for this drug by hyperpolarization as assumed recently by Kreitner [16].)

4. If atrial fibers are partly depolarized artificially they start to show repetitive activity resembling very much the nodal action potentials [10].

5. The membrane of the nodal fibers — and especially of the fibers with a prominent prepotential — is polarized in a potential range in which in the working myocardial fibers a calcium transport system might be activated. Therefore, participation of a calcium inward current in the upstroke of the action potential as well as in the development of the prepotential in fibers of the SA node is very probable. This might explain the sensitivity of these fibers to manganese which is known to have a suppressive effect on the calcium permeability of the membrane. Furthermore, the positive chronotropic effect of adrenaline might be explained by an enhanced calcium inward current leading to a faster slope of the prepotential.

The Effect of Impulse Formation Outside the SA Node on the Behavior of the SA Nodal Fibers

Impulse formation – artificially induced or spontaneous – outside the SA node is called ectopic. Such an ectopic impulse can cause a premature beat. The dominant pacemaker, surrounded by slow-conducting nodal tissue, will be discharged by an ectopic impulse only if it is generated prematurely enough to reach the dominant pacemaker fibers before they discharge spontaneously. As long as the dominant pacemaker is not influenced by the ectopic impulse, the rhythm of the pacemaker is undisturbed and the atrium is activated subsequent to the premature beat with a slightly longer, but exactly compensatory, interval (late atrial premature beats).

If the ectopic impulse is generated earlier in the atrial cycle, the pacemaker in the SA node is discharged and another group of fibers will take over the function of pacemaker for one or a number of beats. The pacemaker shifts over a larger distance within the SA node as the premature impulse comes earlier in the atrial cycle. For a detailed analysis of the effects of atrial premature beats the reader is referred to the studies of Bonke et al. [5], Bonke et al. [6], and Miller and Strauss [21] on the isolated right atrium of the rabbit.

If an impulse from an ectopic pacemaker reaches the border of the SA node, it encounters fibers with a longer refractory period, the perinodal fibers [24], and this becomes more and more pronounced as the impulse penetrates deeper into the SA node. The impulse of very early atrial premature beats will therefore die out in the border of the SA node and only have electrotonic influence on the dominant pacemaker in the center of the SA node [6]. In these cases the rhythm of the dominant pacemaker is practically undisturbed and the atrial premature beat will be an interpolated beat between two spontaneous discharges of the dominant pacemaker in the SA node.

Since the impulse of the premature beat in this case is blocked in the border of the SA node, there is a sinoatrial node entrance block [4, 11, 25]. This conduction block protects the dominant pacemaker.

If ectopic impulse formation continues and a number of atrial premature beats appear, the situation is completely different. The pacemaker in the SA node has lost its dominance, nodal entrance block of varying degree might occur, and part of the SA node might be involved in a re-entry circuit [12]. Therefore, during a series of atrial premature beats or during atrial tachycardia, for instance, induced by a single premature beat [1, 2] or during artificial atrial pacing, the SA node no longer plays a dominant role and resembles the AV node. The effect of artificial drive on the pacemaker activity in the SA node has been investigated by Lange [17] in intact hearts and by Lu et al. [19] in isolated atrial preparations. It turned out that after a period of drive the pacemaker in the SA node did not immediately take over this function but was more or less suppressed. This postdrive suppression was stronger as the period of artificial drive was longer and also appeared to be dependent on the position of the driving electrode. The closer the stimulating electrode to the SA node, the more intensive the postdrive suppression. Lange [17] assumed that the postdrive suppression is — at least partly — due to the liberation of acetylcholine from the terminal vesicles in and around the SA node and the results of her pharmacologic studies on this phenomenon support this assumption. It is also in agreement with the findings of Lu et al. [19] who observed that during overdrive the fibers in the border of the SA node showed some hyperpolarization. In contrast, atrial fibers depolarize when the frequency of stimulation is increased [22].

Some investigators used the interval between the last driven beat and the first spontaneous discharge of the SA node as a measure of the amount of overdrive suppression (sinus node recovery time). However, a number of factors determine this "recovery time," namely the pacing rate, the duration of the pacing, the position of the stimulating electrode, the conduction velocity in the atrium and the SA node, the amount of transmittors — acetylcholine as well as (nor)adrenaline — that are liberated, and of course whether the SA node as a whole is following the stimulation rate or not. At least, it is possible that the first atrial activation after the cessation of the pacing is based on a reentrant beat from the SA node. Some of these factors can be controlled in case of an isolated atrium preparation, but for the human heart in vivo, it is very dangerous, in my opinion, to use the "recovery time" as an indicator of the sinus node function.

In conclusion, the relatively bad conduction properties and the long duration of the action potential of the SA node fibers, protect the SA node against high frequent impulses invading the node from the atrium. Although the blockade of the impulse might occur either at the border of the node or more to the center, it is called in general a sinoatrial entrance block. Once an impulse is generated in the SA node, it is conducted toward the atrium and will excite the atrial fibers. Only if the conduction is disturbed in the border of the node or in the atrium — for instance, because of an increased extracellular potassium concentration — will a sinoatrial exit block occur. In