Br Heart J 1989;**61**:309–15

Review

Does the atrioventricular node conduct?

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It is difficult to be certain when the term "conduction" was first applied to the transfer of atrial activation to the ventricles.[1] In 1894, Engelmann used the word "Leitung", which can be translated as "connection" or as "conduction".[2] In 1906, Tawara described the atrioventricular node, which he termed "Das Reizleitungssystem des Herzens".[3] The mechanism of atrioventricular transmission continued to be a subject of considerable debate.[4-9] There is a summary of the various mechanisms that were thought to explain atrioventricular transmission in Scherf and Cohen's book on the atrioventricular node.[10] Primarily through the work of Hoffman and Cranefield and their associates,[11 12] and to a lesser extent others,[13 14] it became generally accepted that atrial excitation was slowly "conducted" through the atrioventricular node to the His-Purkinje system and the ventricular myocardium.

Hoffman and Cranefield stated that "the excitable cell . . . possesses the same electrical properties as a telegraph cable".[15] Because the "connecting" tissue between the atria and the ventricles was regarded as a series of excitable cells, it followed that the atrioventricular junction was a conduction system. None the less, studies of the complicated structure of the mammalian atrioventricular junction,[14] and the time relation between recorded action potentials from exposed rabbit atrioventricular node[16 17] have not as yet yielded sufficient data to construct a model of the spatial excitation of the atrioventricular node that is analogous to that of the canine and human ventricles.[18 19] The atrioventricular node cannot be mapped with the preciseness required to document the sequence of excitation through this part of the specialised conduction system. Although it seems logical to assume conduction through the atrioventricular node, this claim remains open to question and conjecture. Moreover, some observations[20] suggest that the traditional concept of the atrioventricular junction as a passive cable with varying electrical properties warrants further examination. The concept of the atrioventricular node as an oscillator—that is an unprotected pacemaker—may be a somewhat more flexible and biologically sound explanation of the linear and the non-linear functions of the atrioventricular junction.[21]

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The concept of the atrioventricular node as an unprotected pacemaker is not new. In 1925, Lewis[22] in referring to the work of Mackenzie[23] and Mobitz,[24] stated that, "The structure of the A-V node, and its similarity to the S-A node, has suggested the last as the ventricular pacemaker, and it has been thought that a new and distinct wave may start in this after each systole of the auricle".

Functions of the atrioventricular node

A reasonable starting point from which to consider the possibility of the atrioventricular node as an unprotected pacemaker or oscillator is to examine its three functions: (*a*) synchronisation of atrial and ventricular contraction with appropriate and variable delay depending on the heart rate,[25] under conditions of varying autonomic nervous system influences and in different species,[26 27] (*b*) protection of the ventricles from excessive atrial rates when there is atrial arrhymia,[28 29] and (*c*) the role as a latent escape pacemaker in the event of atrioventricular block or atrial bradycardia or arrest.[30]

The atrioventricular node can act as a passive pacemaker and deductive reasoning supports the concept of the atrioventricular node as an electrotonically modulated pacemaker during atrial fibrillation.[20] So the question arises as to whether the atrioventricular node, in addition to its pacemaker function, needs to act as a conduit with varying resistive and capacitive properties[15] to perform the three functions or can all functions of the atrioventricular node be explained on the basis of the assumed pacemaker characteristics?

Atrioventicular node as an oscillator (pacemaker)

In 1929 Van der Pol and Van der Mark proposed that the heart beat could be viewed as a relaxation oscillator.[31] In 1940 Bethe suggested that other

rhythmic phenomena of the heart, such as a bigeminal rhythm, should also be regarded as oscillatory movements.[32] A relaxation oscillator is best described as a condenser that is periodically discharged by the ignition of a neon tube. The frequency of a relaxation oscillator is dependent on the energy supplied and can be increased or decreased by certain external periodic electrical phenomena of small amplitude, such as a sine wave current. In 1973 Van der Tweel *et al* showed that the sinus node of an isolated rat heart could be synchronised the same way as a relaxation oscillator.[33] These observations strongly support the notion that cardiac pacemaker cells may behave, in a physical sense, like relaxation oscillators and, apart from its intrinsic firing rate, the atrioventricular node may not be so different from the sinoatrial node.[34] Grant first suggested that the atrioventricular node can be regarded as an oscillator.[21] Subsequent studies supported this concept.[35 36] More recently Schamroth *et al* presented evidence that an ectopic pacemaker may be regarded as an oscillator that is synchronised (entrained) by the electrotonic modulation generated by the sinus impulse.[37]

ATRIAL FIBRILLATION

In 1983 Cohen *et al* developed a quantitative model for the ventricular response during atrial fibrillation.[38] In this model the atrioventricular junction is regarded as the equivalent of a single pacemaker cell characterised by a refractory period and spontaneous phase 4 depolarisation. In 1986 Van der Tweel and co-workers provided experimental evidence that the atrioventricular node may indeed act as a periodically perturbed biological oscillator.[39]

If we assume that the atrioventricular node acts as an oscillator, can its functions, outlined above, be served and its role in control of cardiac rhythmicity be explained? It is reasonable to assume that the random ventricular rhythm during atrial fibrillation can be the result of electrotonic modulation of phase 4 of the transmembrane action potential[20 38] of the atrioventricular node by randomly spaced atrial excitations.[40-42] Instead of postulating concealed conduction of atrial impulses into the atrioventricular junction[43-45] during atrial fibrillation, let us assume that, depending on the random strength, direction, and timing, the electrotonic effect of the atrial excitation either accelerates diastolic depolarisation of the atrioventricular nodal pacemaker (and thus shortens the RR interval) or decelerates the diastolic depolarisation (hyperpolarise) (and thus lengthens the RR interval) (fig 1). In such a model the ventricular rate and rhythm during atrial fibrillation

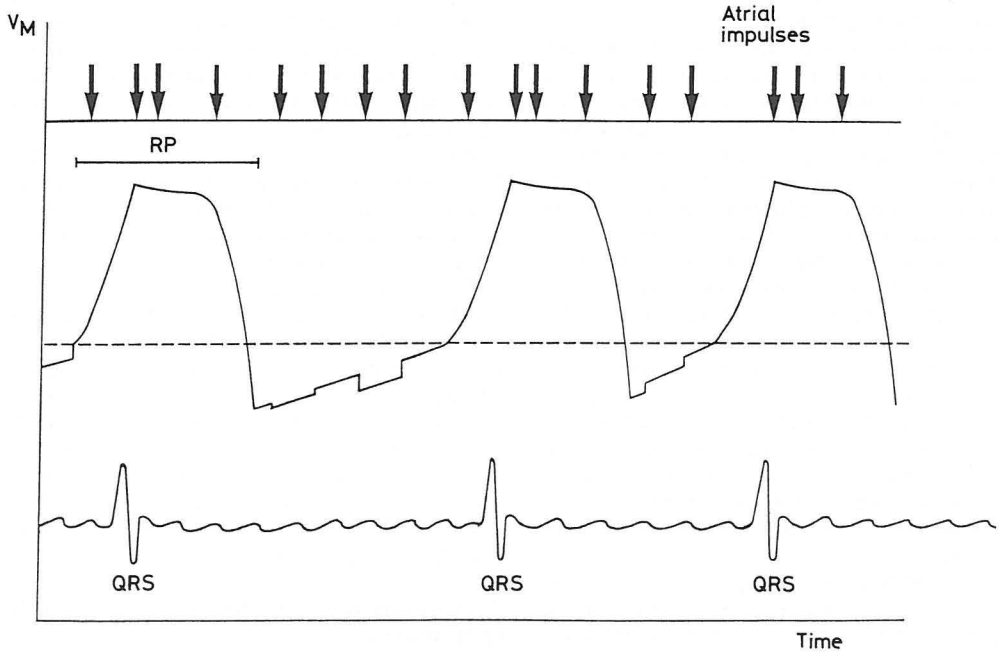

Fig 1 *Hypothetical model of the atrioventricular nodal pacemaker during atrial fibrillation. Depending on strength, timing, and direction of the atrial impulses, diastolic depolarisation can be speeded up or slowed down (hyperpolarisation) during atrial fibrillation. This explains why the RR intervals vary randomly. This model is an extension of the model of Cohen et al.[38]; RP, refractory period; VM, voltage of hypothetical monophasic action potential.*

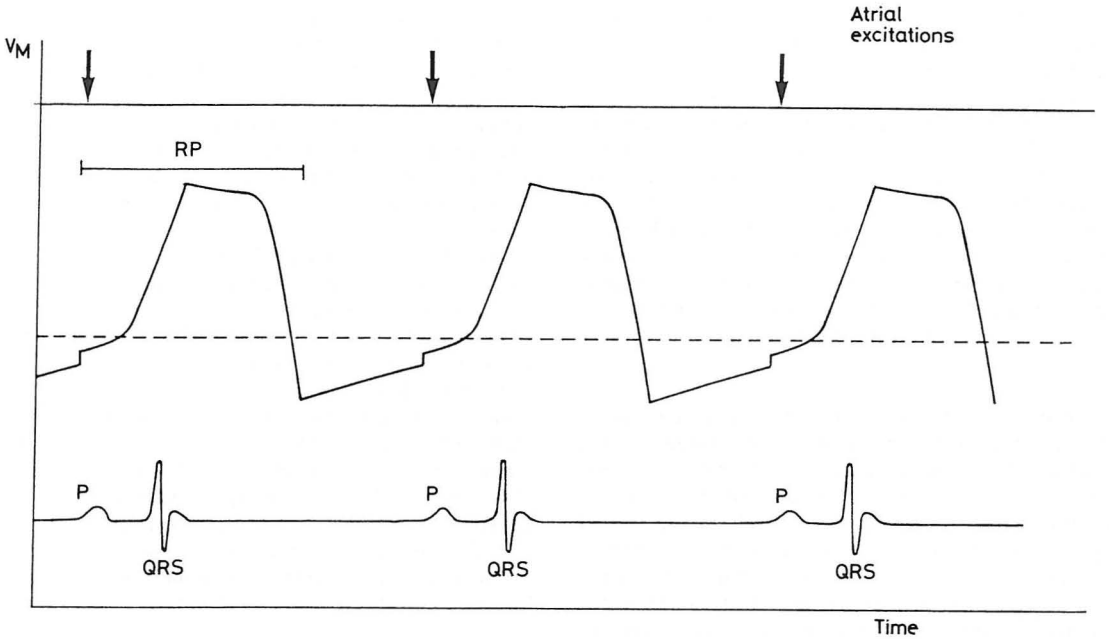

Fig 2 *Hypothetical model of the atrioventricular nodal pacemaker during sinus rhythm. The ventricular rate and PR interval depend on the sinus rate and the slope of phase 4 depolarisation of the atrioventricular nodal pacemaker. During sinus rhythm or any other organised atrial rhythm the electrotonic effect of the atrial excitations is constant. Varying PR intervals during sinus arrhythmias, long PR intervals of atrial extrasystoles or, for instance, concealed conduction of a non-transmitted P wave can be explained by this model.*

would depend on the random electrical properties of the fibrillating atria[42] and the refractoriness and the intrinsic rate of the atrioventricular nodal pacemaker. The rate of the atrioventricular nodal pacemaker in turn could be increased or decreased by the autonomic nervous system.[46 47] Similarly, anterograde block during right ventricular pacing in the presence of atrial fibrillation might be attributed to concealed retrograde conduction of the ventricular depolarisations with overdrive suppression of the atrioventricular nodal pacemaker.[20 48]

Entrainment of the atrioventricular node

If we assume that the atrioventricular node acts as a biological pacemaker or oscillator, then when atrial rhythms are organised atrioventricular "coupling" could result because of synchronisation (entrainment) of the atrioventricular node by the electrotonic spread of the atrial wave of excitation (fig 2).

In 1940 Katz and Schmitt described the electric interaction between two adjacent nerve fibres, which they called "synchronisation".[49] In 1947 Segers *et al* first referred to possible synchronisation of the atrioventricular nodal pacemaker, namely a fixed temporal relation between the atria and ventricles resulting in isorhythmic dissociation.[50] This phenomenon is known as acchrochage, a term which Segers introduced in 1946, when he discovered two fragments of a frog's heart that beat in phase when they were brought into physical contact.[51]

DEFINITION OF ENTRAINMENT

Jalife and Michaels defined entrainment as the coupling of a self sustained oscillatory system (such as a pacemaker) to an external forcing oscillation with the result that either both oscillations have the same frequency or the frequencies are related in a harmonic fashion.[52] Winfree defined entrainment as "The locking of one rhythm to another, with N cycles of the one matching M cycles of the other" and suggested that cardiac pacemaker cells may be synchronised by electrotonic interaction.[53] This ability of most non-linear oscillators to entrain or synchronise rests on their time-dependent sensitivity. A probable cellular electrophysiological mechanism responsible for entrainment and synchronisation is an alteration of the rate of phase 4 depolarisation of pacemaker cells. Van der Tweel *et al* in 1973 showed that a pacemaker does not need to be ectopic to be synchronised or entrained.[33] After the introduction of the concept of entrainment in cardiac electrophysiology by Segers *et al*,[50 51] Moe *et al* sys-

tematically investigated the electrophysiological mechanisms of synchronisation and entrainment of cardiac pacemakers.[54-58]

Waldo *et al* introduced the term "transient entrainment" to explain the observation that the rate of a tachycardia can be increased by a more rapid electronic pacing rate.[59] This form of entrainment[60] differs from the original concept in that the pacemaker rate can not only be increased but also decreased. The concept that we believe to be most appropriate, based on available evidence, is that of the entrained biological oscillator as defined by Winfree[53 61] and Jalife and Michaels.[52]

SINUS RHYTHM

Entrainment of the atrioventricular nodal pacemaker during sinus rhythm by an atrial impulse would explain the paradoxically comparatively short PR intervals in hearts of large mammals such as elephants and whales[62-64] which have much larger atrioventricular nodes than those of human beings.[65 66] If during sinus rhythm the atrioventricular node acts as an entrained pacemaker or oscillator, atrioventricular nodal delay need no longer be dependent on the size of the atrioventricular node, or cable length, nor would the short atrioventricular nodal delay in such large hearts conflict with the expected protection against high atrial rates.[28 29] This assumption would be strengthened were the atrioventricular nodal pacemaker located at the NH-H border[67] so that it would promptly activate the His-Purkinje system. The presence of monophasic action potentials with a distinct diastolic depolarisation in the NH-region[11 17] localises the atrioventricular nodal pacemaker to that specific area within the atrioventricular node.

The concept of a biological oscillator also explains the shortening of the PR interval during sinus tachycardia induced by sympathetic stimulation or physical exercise. In contrast with atrial tachycardia or rapid atrial pacing (see below), the sympathetic drive not only affects the frequency of the sinus pacemaker and the atrial rate, but also the intrinsic rate of the atrioventricular nodal pacemaker and thus the rate of rise of phase 4 depolarisation. The steeper phase 4, the earlier is the threshold potential reached and the shorter the PR interval (fig 2).

RETROGRADE (VENTRICULOATRIAL) CONDUCTION

In 1959 Scherf used the concept of electrotonic spread to explain retrograde conduction with a relatively short RP interval in the presence of complete atrioventricular block.[68] Since the strength of the electrotonic spread of the ventricular excitation wave may well exceed that of the atrial excitation wave it seems logical that retrograde (ventriculoatrial) "conduction" may be present during partial or complete anterograde (atrioventricular) block.[69 70] This concept could also explain why structural damage of the atrioventricular junction impairs anterograde conduction more than retrograde conduction. In this setting, however, the geometry of the atrioventricular junction may also be important. If we assume that electrotonic spread can result in retrograde conduction in the presence of atrioventricular block, it is reasonable to expect that it also operates in the absence of atrioventricular block. Similarly, if the electrotonic spread is responsible for retrograde conduction, it may also be the mechanism of anterograde conduction.

Also the findings by Akhtar *et al* that anterograde (atrioventricular) conduction can be affected by retrograde (ventriculoatrial) conduction, and the other way round,[71-73] can be explained by electrotonic spread. For instance, a concealed retrogradely conducted ventricular impulse could cause an early resetting of the atrioventricular nodal pacemaker and thus facilitate anterograde conduction.

ATRIAL TACHYCARDIA

If the atrioventricular nodal pacemaker is electrotonically coupled to the sinus node by atrial excitation what is the effect of atrial tachycardias or rapid atrial pacing on atrioventricular nodal function? Atrial arrhythmias with high rates could be blocked by either an insufficiently strong electrotonic effect on phase 4 depolarisation in the presence of a relatively slow intrinsic rate of the atrioventricular nodal pacemaker or by entrainment in a higher harmonic fashion[35 52] as, for example, during atrial flutter with atrioventricular block. Van der Tweel *et al* have shown that this manifestation of entrainment operates at the level of the sinoatrial node of isolated rat hearts.[33] There is probably an upper limit to which the intrinsic oscillatory rate of the atrioventricular nodal pacemaker can be increased by an artificial pacemaker or an ectopic focus. At that point its rate can no longer be enhanced through entrainment by the artificial atrial pacemaker. Long PR intervals, and, subsequently, Wenckebach periodicity may result when the atrial and the atrioventricular nodal pacemaker rates are out of phase. Wenckebach type I atrioventricular block may also result from damage below the assumed location of the atrioventricular nodal pacemaker, from too low an intrinsic rate of the atrioventricular nodal pacemaker, or from impaired conduction in the His-Purkinje system. In the absence of sympathetic influences the rate of phase 4 depolarisation does not increase and it takes longer to reach threshold. The coupling of the ventricles to the atria occurs at the

moment the electrotonic spread of the atrial excitation reaches the atrioventricular nodal pacemaker. An impulse arriving early in diastole or in the presence of a slow phase 4 depolarisation, or both, will result in a long PR interval. On the contrary, an impulse arriving late in diastole or in the presence of a fast phase 4 depolarisation, or both, will result in a short PR interval (fig 2).

ACCESSORY PATHWAYS

In the presence of a Kent bundle or other accessory pathways the concept of the atrioventricular node as an oscillator would change the current notion that competition between two conduction pathways with different electrophysiological properties is the mechanism of Wolff-Parkinson-White syndrome.[74-76] The competition (fusion) would rather be between a passive, at times rapidly conducting pathway and a synchronised, entrained biological oscillator located in the atrioventricular node. Conduction through the accessory pathway that results in ventricular excitation could either cause overdrive suppression of the atrioventricular node and thus force the atrial impulse to procede along the accessory pathway, or it could reset the atrioventricular nodal pacemaker and activate the atrial myocardium, resulting in an atrioventricular reentrant tachycardia.

Conclusion

There can be no doubt about the importance of electrotonus as the mechanism of otherwise inexplicable arrhythmias.[77-80] In this presentation the atrioventricular node is regarded as a biological oscillator and electrotonus induced by organised atrial or ventricular excitation as the mechanism by which the oscillator can be entrained.

The concept of the atrioventricular node as an oscillator/pacemaker influenced by electrotonus is in keeping with the functions of the atrioventricular node and offers a rational explanation for the varying atrioventricular nodal delay during sinus rhythm, the protection the atrioventricular node affords in the presence of atrial tachycardias and fibrillation, and for atrioventricular nodal automaticity as an escape mechanism. The concept accords with clinical and experimental observations that classically have been attributed to the "conducting" properties of the atrioventricular junction. It also offers a rational explanation for the relatively short PR intervals in large mammals such as elephants and whales, as well as for several atrioventricular "conduction" abnormalities and arrhythmias. In fact, the assumption that conduction and automaticity are properties of the atrioventricular node tends to complicate rather than to clarify the understanding of atrioventricular nodal function under varying physiological and pathological influences.

The question whether the atrioventricular node conducts in the traditional meaning of the word warrants further investigation.

This study was supported by the Wijnand M Pon Foundation, Leusden, The Netherlands.

We thank Dr Suzanne B Knoebel for her contribution to the concept and the preparation of this paper.

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