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Role of the Atrioventricular Node in Atrial Fibrillation

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Atrial fibrillation (AF) is probably the most common cardiac arrhythmia in humans, particularly in the elderly (1–3). The irregularity and inequality of the heart beat first described by Hering in 1903 were, and continue to be, the landmark of the clinical diagnosis of AF (4,5). Sir Thomas Lewis (6) observed the gross irregularity of the arrhythmia and stated "the pauses betwixt the heart beats bear no relationship to one another." Thanks to work of Lewis (7), Mackenzie (8), Wenckebach (9), and others, the clinical syndrome of AF became well established, and gradually the pathophysiologic mechanisms involved were also recognized (10). In 1915 Einthoven and Korteweg (11) studied the effect of heart cycle duration on the size of the carotid pulse and concluded that the strength of the heart beat was related to the duration of the preceding cycle. Later we repeated those observations by studying in a quantitative fashion the effects of randomly varying RR intervals on the contractions of isolated Langendorff perfused rat hearts (12). Recently Hardmann confirmed the complicated relationship between the randomly irregular rhythm and left ventricular function in patients with AF, confirming the involvement of postextrasystolic potentiation and restitution (13).

Animals may also develop AF (14,15). Indeed, Lewis (7) observed the arrhythmia in an open-chest horse and used this observation to establish that the irregular pulse noticed in humans was due to fibrillation of the atria. Until the 1950s, observations on AF were limited to its etiologic, clinical, and surface ECG manifestations. The beginning of the computer era enabled several groups of investigators to analyze the ventricular rhythm during AF in a more quantitative fashion (16–18). The results of these studies were fascinating and allowed for the development of theories on the behavior of the atrioventricular (AV) node during AF. Sophisticated computer techniques allowed Moe and Abildskov (19,20) to simulate atrial electrical activity during AF, and they formulated the so-called multiple wavelet theory, which was in 1985 supported by experimental evidence (21). Parallel to the growing insight into the electrical behavior of the atria during AF and into the corresponding ventricular rhythm, sophisticated experimental methods were designed to study AV nodal electrophysiology in a variety of circumstances, including induced AF (22,23).

This chapter reexamines some of the established concepts of AV nodal function (24) because comparative physiology of the AV node and some specific electrocardiographic observations in patients with AF have demonstrated inexplicable flaws in the current theories of AV nodal function. Alternate mechanisms, which till now have hardly been considered as a basis for explaining AV nodal function during AF, will be discussed.

In the first edition of this book (25) we postulated that the AV node, rather than acting as an intrinsic part of the cardiac conduction system, is primarily a pacemaker subject to electrotonic influences from other areas in the heart. However, as will be made clear in this chapter, the pacemaker theory cannot explain all clinical phenomena inherent to AF. So a new model based on recently discovered cellular electrophysiologic principles (26,27) has been developed and will be presented.

DEFINITION

Atrial fibrillation has been defined by a WHO/ISFC Task Force (28) as "an irregular, disorganized, electrical activity of the atria. P waves are absent and the baseline consists of irregular wave forms which continuously change in shape, duration, amplitude, and direction. In the absence of advanced or complete AV block, the resulting ventricular response is totally irregular (random)." This definition is applicable to routine medical practice, when we are usually satisfied that the atria are fibrillating if the ventricular arrhythmia fills the criterion of being totally irregular (random). This does not imply that during AF nonrandom ventricular rhythms cannot occur, but in case of a random ventricular ventricular rhythm and a typical aspect of the baseline of the ECG one can be certain that the patient has true AF.

Several investigators have studied the electrical activity of the atria during AF (29,30) and were able to demonstrate the chaotic character of the atrial electrical activity. Using signal analysis of the atrial electrogram for the study of AF (31), we found a random pattern of the intervals between the zero crossings of the atrial deflections with a rate between 300 and 600/min. However, not only does the sequence of the recorded atrial signals display a random pattern during AF, the form and strength of the recorded signals also fail to show any repetition. Thus, the AV node receives or is surrounded by impulses that are random in time and almost certainly also in form, strength and direction and this results in a random duration of the RR intervals (32,33).

THE VENTRICULAR RHYTHM

The (random) pattern of the ventricular rhythm during AF can be demonstrated by means of a serial autocorrelogram (SAC), as illustrated on the right-hand side of Fig. 1. The SAC is obtained by the measurement of the duration of the RR intervals. Each RR interval duration is correlated with itself, then with the duration of the next RR interval and subsequently with RR interval durations that are a given number of RR intervals ahead. Correlation coefficient number 0 is the result of correlating the duration of each RR interval with itself and consequently equals +1. Correlation coefficient 1 is the result of correlating the duration of each RR interval with the next and its value depends on the measure of relation between this two sets of RR interval durations. Similarly, correlation coefficient 10 represents the relation between the durations of all RR intervals that are 10 intervals apart, 20 represents all those that are 20 intervals apart, etc. In a random process all correlation coefficients greater than 0 have values that are statistically not significantly different from 0, and, consequently, if the values of successive correlation coefficients of the RR intervals do not differ from 0, that rhythm may be called random. In Fig. 1, derived from a patient with AF (32), it can be seen that before and after the administration of digitalis, the correlation coefficients do not differ from 0 and thus the ventricular rhythm under both circumstances is, by definition, random. The histogram (left side

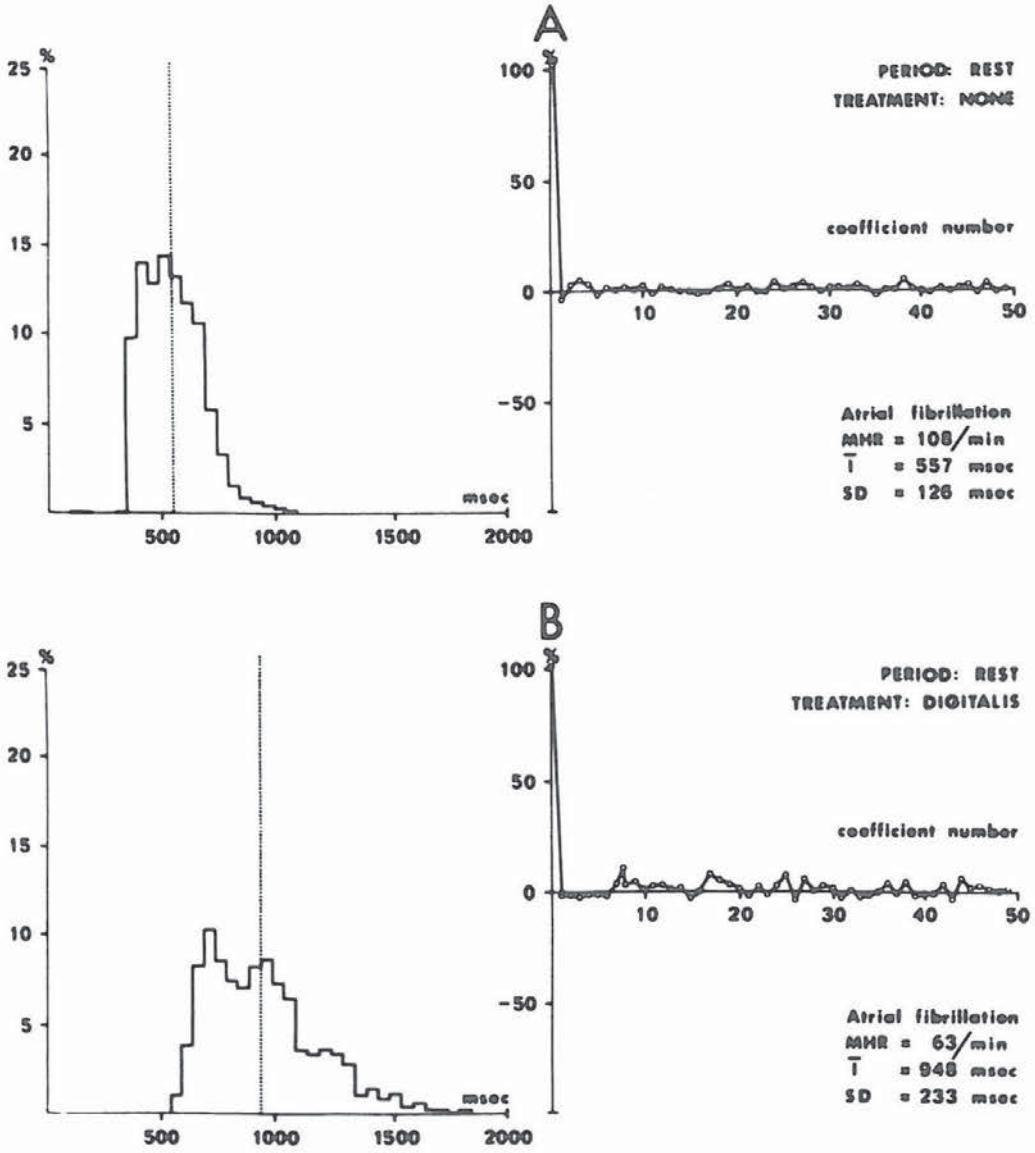

FIG. 1. Histogram and serial autocorrelogram (*SAC*) of a patient with atrial fibrillation without **(A)** and with **(B)** digitalis treatment. The SAC is unchanged, thus the ventricular rhythm remains random despite change in form and shift to the right of the histogram. For further details, see text. (From Bootsma et al. ref. 32, with permission.)

of Fig. 1) shows a decrease in ventricular rate produced by digitalis, but the degree of irregularity expressed as the dispersion of RR intervals (33) or coefficient of variation (CV) (34) remains constant. We will return to this later.

The random ventricular rhythm in AF can also be described as a renewal process or as a "point process without memory." A point process is a process in which the duration of the event—the R wave for instance—is short compared with the interval between events (the RR Interval). Well-known examples of point processes are the emissions from a radioactive source, the action potentials of a nerve fiber, coal mining disasters, and wars (35). In AF the duration of a forthcoming RR interval can never be predicted. After each event the process starts anew, totally disregarding its past.

Another way to display the ventricular rhythm during AF makes use of a so-called interval plot (Fig. 2). The duration of each RR interval is plotted against its sequential

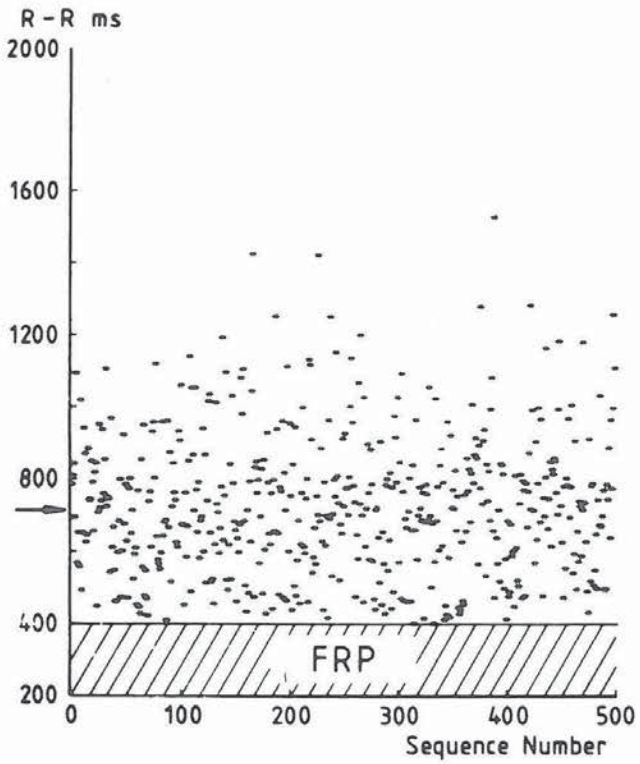

FIG. 2. Interval plot of 500 RR intervals of a human patient with atrial fibrillation. Each dot represents one RR interval. The arrow indicates the median RR interval. For further details, see text. (From Meijler and Van der Tweel, ref. 36, with permission.)

number. The RR interval plot does not contain information that is not present in the histogram and SAC, but it nicely illustrates the functional refractory period (FRP) of the AV junction as well as the maximal duration of the RR intervals of that particular patient at the time the recording was obtained (36).

In 1970 we questioned (32) if the AV node has a role to play in determining the degree of irregularity of the ventricular rhythm during AF since pharmacologic or physical interventions that affect the ventricular rate during AF do not interfere with the random pattern of the ventricular rhythm. We concluded that the primary cause of the randomly irregular ventricular rhythm must reside in the fibrillating atria.

DECREMENTAL CONDUCTION

The slow ventricular response and its persistent randomness during AF have been explained by concealed conduction in, and the refractory period of, the AV node. In 1948, Langendorf (37) introduced the term *concealed conduction* into clinical electrocardiography. The WHO/ISFC Task Force (28) defined concealed conduction as: "partial penetration of an impulse into the AV conduction system or a pacemaker-myocardial junction, which exerts an influence on subsequent impulse formation or conduction or both." The term has been redefined by Fisch (38) as "the presence of incomplete conduction coupled with an unexpected behavior of the subsequent impulse." Concealed conduction is a concept, something that one cannot see but that has to be inferred from the aftereffect of a blocked impulse. Concealed conduction in the AV node during AF, among others, is assumed to result from decremental conduction (24,39). Hoffman and Cranefield (40) described decremental conduction as "a type of conduction in which the properties of the fiber change along its length in such a manner that the action potential becomes pro-

gressively less effective as a stimulus to the unexcited portion of the fiber ahead of it." In a recent article Watanabe and Watanabe (24) strongly advocated the concept of decremental conduction but, as we will show, this concept is at odds with a number of ECG symptoms that can be observed during AF.

In 1965, Langendorf et al. (41) postulated that concealed conduction in the AV junction could explain the characteristics of the ventricular rate and rhythm during AF. Several subsequent investigators used the concept of decremental conduction to explain concealed conduction within the AV node during experimentally induced AF (24,42,43). The effects of drugs such as digitalis (44), quinidine (45), and beta-blockers (46) on the ventricular rate in AF were also explained by this theory, although the sometimes observed so-called regularizing effect of verapamil and other Ca^{2+} antagonists remained less well understood (47).

ELECTROTONIC MODULATION OF AV NODE PACEMAKER ACTIVITY DURING ATRIAL FIBRILLATION

The majority of clinical investigators seems satisfied with the decremental conduction concept, although Grant (48) in 1956 and James and his group (49) in 1977 suggested alternate explanations based on the theory that atrial impulses may modify an intrinsic pacemaking function of the AV node rather than being directly, albeit more slowly, conducted through it.

The concept of the AV node as an unprotected pacemaker is not new. As early as 1925 Lewis (50) postulated that AV nodal function could be interpreted in another fashion than as conduction: "The structure of the A-V node and its similarities to the Sino-Atrial (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." In this statement, Lewis considered AV nodal function during sinus rhythm or at least during organized "auricular" activity as a form of pacemaker activity.

In 1929, two Dutch physicists (51), Van der Pol and Van der Mark, proposed that the heart beat could be viewed as a relaxation oscillator. A relaxation oscillator is best described as a condenser that is periodically discharged by the ignition of a neon tube. An important characteristic of an oscillator is that it can be synchronized by external electric forces.

Van der Tweel et al. (52) showed that the sinus node as well as the AV node of an isolated rat heart can be synchronized in the same way as a relaxation oscillator. Many years later we demonstrated that the function of the canine AV node can be described as a periodically perturbed biologic oscillator (53). Perturbation and/or synchronization of an oscillator can be electrophysiologically translated into entrainment of a pacemaker (54). Segers et al. (55) first referred to possible synchronization of the AV nodal pacemaker resulting in a fixed temporal relation between the atria and the ventricles to explain an isorhythmic dissociation during complete heart block in patients. Jalife and Michaels (56) 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 both frequencies are related in a harmonic fashion. Winfree (57) defined entrainment as "the locking of one rhythm to another, with N cycles of the one matching M cycles of the other."

A possible electrophysiologic mechanism responsible for entrainment or synchronization of pacemaker cells is an alteration of the rate of their phase 4 depolarization. It might

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