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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.

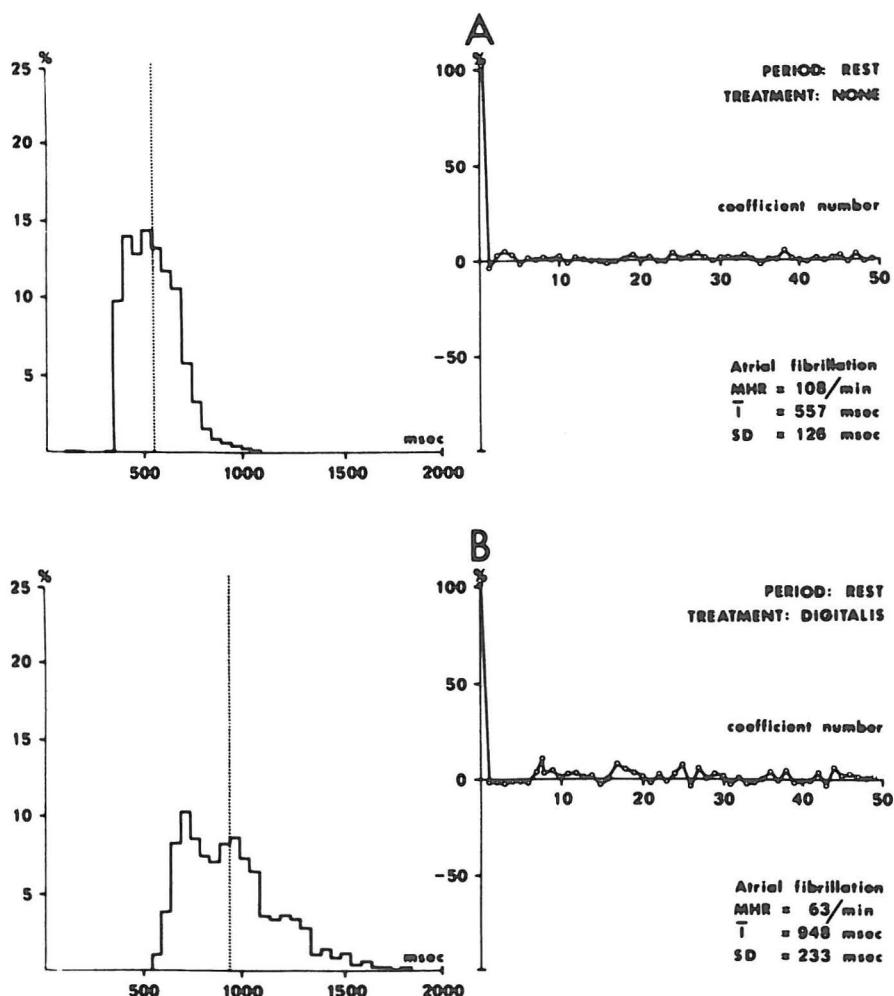
## DEFINITION

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

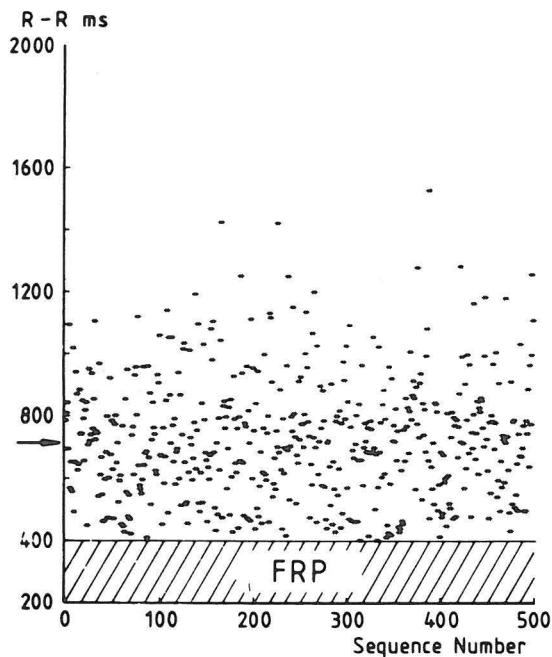


**FIG. 1.** Histogram and serial autocorrelogram (SAC) of a patient with atrial fibrillation without (A) and with (B) digitalis treatment. The SAC is unchanged, thus the ventricular rhythm remains random despite change in form and shift to the right of the histogram. For further details, see text. (From 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  $\text{Ca}^{2+}$  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

thus be considered plausible that during sinus rhythm, the AV node, like the SA node, behaves as an oscillator or pacemaker that is entrained by the atrial depolarization sparked by SA firing (58,59).

Cohen et al. (59) developed a quantitative model along these lines to also describe the ventricular response during AF. Electrotonic modulation of phase 4 depolarization of a pacemaker cell equivalent, by randomly occurring atrial impulses of random strength and duration and coming from random directions, could thus explain both the random and the slower ventricular rhythm during AF.

Vereckei and coworkers have challenged the AV nodal pacemaker hypothesis (58–60). Utilizing an open-chest dog model they examined the effect of ventricular pacing at different cycle lengths during induced AF. They were unable to consistently reproduce observations seen in humans, that is, that anterograde conduction in AF can be blocked by ventricular pacing with interstimulus intervals considerably longer than the shortest RR intervals during anterograde conduction. Although they concluded that their results failed to support the modulated pacemaker hypothesis, they did concede that their data did not totally refute this hypothesis. Indeed, their results show that overdrive suppression resulted in a varying return cycle length which is in agreement with our observations in patients (61). Moreover they used open-chest dogs with induced atrial fibrillation and flutter. Artificial AF may or may not simulate true AF in dogs (62), let alone in patients.

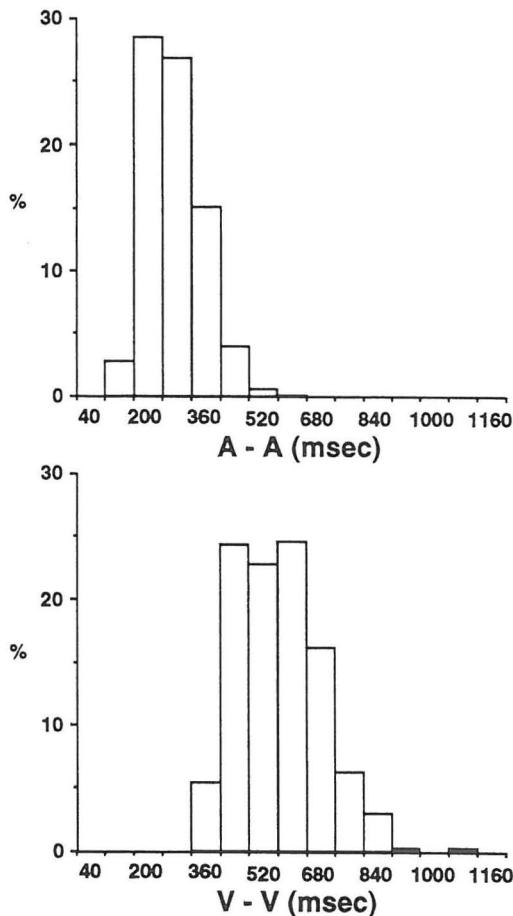
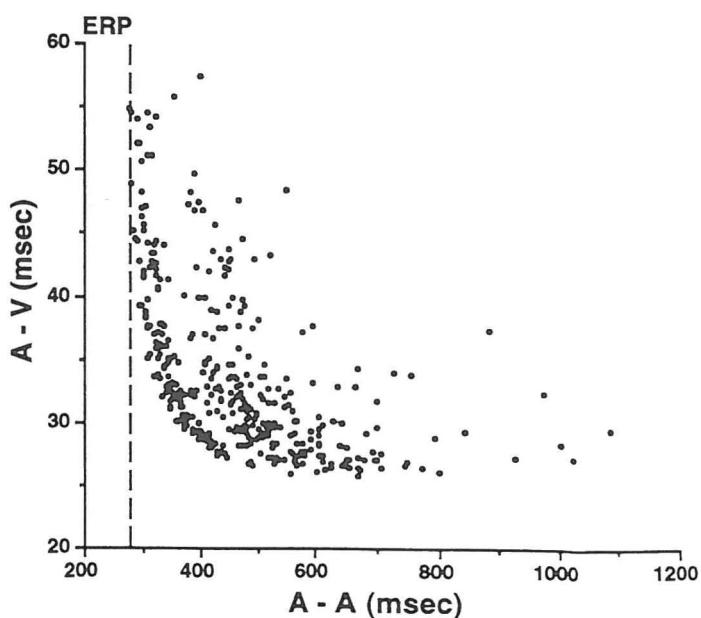
### ELECTRONIC MODULATION OF AV NODAL PROPAGATION

During AF the AV node need not be a pacemaker with spontaneous phase 4 depolarization to be electrotonically modulated by the atrial impulses. Antzelevitch and Moe (63) have shown that in segments with stable resting membrane potentials, nonconducted impulses can exert an inhibitory effect on the electrotonically mediated transmission of subsequent impulses or facilitate propagation when two subthreshold potentials occur in close succession. This form of electrotonic modulation may be responsible for the dynamic changes in AV nodal propagation that lead to the totally irregular ventricular rhythms in AF.

This idea has been tested using a computer model of the AV node, consisting of a linear array of nine cells (64). Two cells represented the atrium, five the AV node, and two the ventricles. The cells were connected by appropriate coupling resistances. During regular atrial pacing, the model reproduced very closely the frequency dependence of AV node conduction and refractoriness. In addition extra atrial impulses concealed within the AV node led to electrotonic inhibition and blockade of immediately succeeding impulses. During simulated AF, the random variations in the atrial intervals yielded random variations in the ventricular intervals but, as in the real life situation, there was no scaling; that is, ventricular intervals were not multiples of the atrial intervals. As such the model simulated the statistical behavior of the ventricles during AF, including (a) the ventricular

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**FIG. 3.** Electrotonic modulation of the AV nodal propagation curve. **a:** The upper histogram represents the distribution of the random atrial rhythm (A-A) supplied to the system; the lower histogram represents the (also random) ventricular rhythm (V-V) obtained. **b:** Each dot represents the conduction time (A-V) in msec of every successfully conducted atrial impulse, plotted against its A-A interval. ERP = effective refractory period. Note the smearing of the A-V intervals. For further details: see text. (From Meijler et al., ref. 64 with permission.)

**a****b**

rhythm was random; and (b) the coefficient of variation (CV) of the ventricular rhythm was constant at any given ventricular rate. The random atrial intervals resulted in complex patterns of AV node concealment. Consequently the effects of electrotonic modulation were also random which resulted in a smearing of the AV node propagation curve, Fig. 3. During AF, electrotonic modulation acts in concert with the frequency-dependence of AV nodal conduction which results in the typical complex patterns of the ventricular intervals. Finally, similar to what has been shown in patients, regular pacing of the right ventricle at the appropriate frequency led to blockade of nearly all anterograde conduction. Electrotonic modulation of AV nodal propagation seems to fulfill most if not all electrocardiographic requirements of AF (64).

## COMPARATIVE ASPECTS OF ATRIOVENTRICULAR NODAL FUNCTION

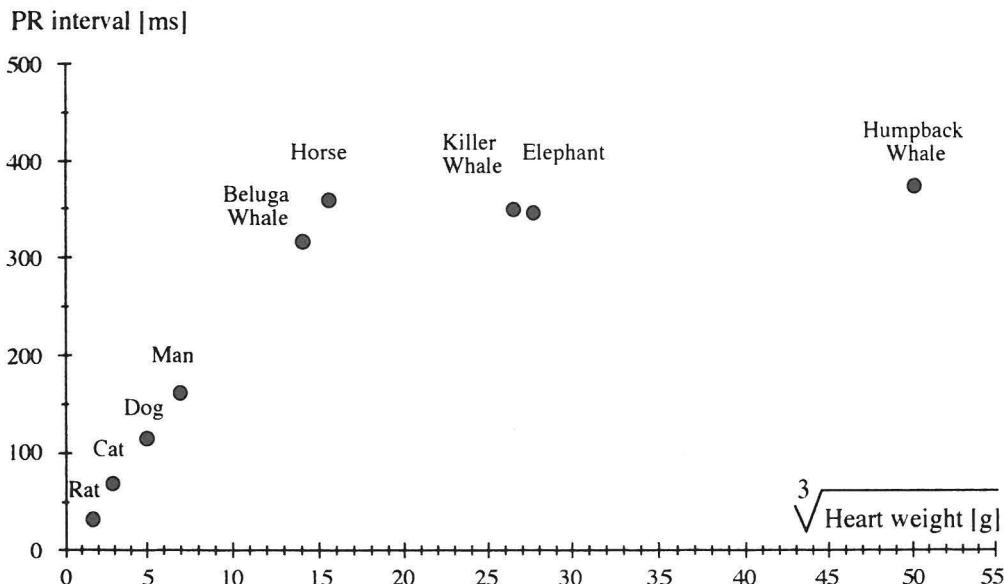
### Sinus Rhythm

Waller in 1913 (65) studied comparative physiology and drew attention to the differences in the "auriculo-ventricular" interval in dogs, humans, and horses. Clark (66) in 1927 studied PR intervals in animals of different sizes and noted the small differences between PR intervals compared to the differences in body size. A systematic listing of PR intervals versus body size shows a comparatively short PR interval in hearts of large mammals and a long PR interval in hearts of small mammals (42,67). Despite differences in detail, the overall architecture and microstructure of all mammalian hearts are essentially similar. Whether the source is the mouse or the whale, cardiac muscle is composed of individual cells that are relatively uniform in diameter, approximately 10 to 15  $\mu\text{m}$  (68). This similarity applies to the morphology of the mammalian AV node-His system as well. Both macroscopically and microscopically the structural arrangement of the mammalian AV conduction system tends to be similar, while the size of the heart varies greatly from species to species (69).

Conduction velocity depends largely on cell (fiber) diameter (70,71). Assuming a more or less constant cell-to-cell resistance, it is unlikely that with increasing length or diameter of the His bundle and bundle branches the known conduction velocity of approximately 2.5 m/sec will increase significantly (72). However, Pressler (73) found a substantial difference of conduction velocity in Purkinje fibers in cats and sheep, although not enough to explain the small difference in PR interval between, for instance, a rat and an elephant (67).

These observations suggest that in a large mammalian heart such as that of the elephant or whale the relative contribution to the AV conduction delay by the AV node or other components of the AV conduction system may be different from that of the heart in smaller mammals, for instance, the human, dog, or rabbit. For example, in the adult blue whale with a His bundle and branches that may be well over 1 m in length from their origin at the distal end of the AV node to their terminal ventricular ramifications, approximately 400 msec will be required for the impulse to cover that distance alone, assuming a conduction velocity of about 2.5 m/sec. Yet the PR interval in the elephant and humpback whale does not exceed 400 msec (67,74–78).

Therefore the AV node, although anatomically present in large mammals and physically larger than in smaller mammals (69,79), would not be expected to create a substantial part of the delay of AV transmission during normal sinus rhythm, even if conduction velocity in the His bundles was greater than 2.5 m/sec. Figure 4 shows that the PR inter-

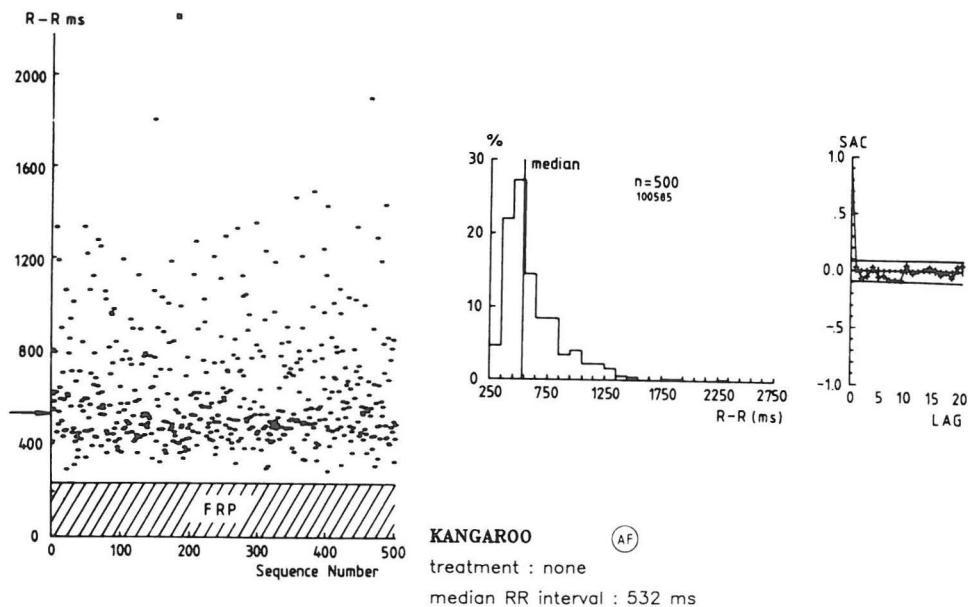


**FIG. 4.** S-shape relationship between PR interval and third root of heart weight. Values obtained from Altman and Dittmer (100). (From Meijler et al., ref. 78, with permission.)

val in a variety of mammals follows an S-shaped relationship when plotted against the third root of heart weight (42,67,77,78). This in itself asks for an explanation (80). If indeed, as can be inferred from Fig. 4, in larger mammals the contribution of the AV nodal delay to the PR interval is proportionately less than in smaller animals, it is difficult to explain the mismatch between the PR interval and heart weight from accepted theories of decremental conduction in the AV node (42,80). At the same time one should realize that nobody has ever reliably measured the conduction velocity in the His-Purkinje system in mammals larger than humans. Therefore any explanation of the fascinating disproportionality between heart size and PR interval in large mammals is based on speculation rather than facts (24,67).

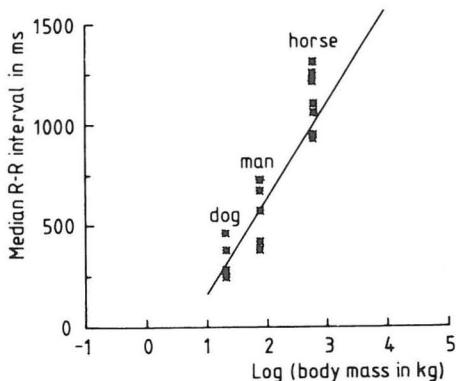
### Atrial Fibrillation

Veterinarians are well aware of the frequent occurrence of AF in large dogs (15) (usually with mitral valve disease) and horses (16,81–83). Indeed, as mentioned earlier, the relationship between fibrillating atria and a totally irregular ventricular rhythm was first demonstrated by Lewis (7) in 1912 in a horse. Moe's (20) multiple wavelet theory states that AF is maintained by the presence of a number of independent wavelets that wander randomly through the myocardium around islets or strands of refractory tissue. In order for AF to be maintained, Moe's theory requires a critical mass of atrial tissue. It is of interest that, in keeping with Moe's hypothesis, spontaneous AF is hardly ever observed in smaller mammals (82). Figure 5 demonstrates a once-in-a-lifetime observation: the interval plot, SAC, and histogram of the ventricular rhythm of a kangaroo with AF. This observation lends further credence to the concept that AF may occur in the heart of any mammal if Moe's conditions are fulfilled (20,21), i.e., a sufficient number of cells involved and/or a sufficient degree of electrical inhomogeneity.



**FIG. 5.** Interval plot, SAC, and histogram of a kangaroo with AF. *FRP*, functional refractory period. The arrow indicates the median RR interval. For further details, see text. (From Meijler et al., ref. 36, with permission.)

Figure 6 shows median RR interval duration versus log body mass in kilograms in dogs, humans, and horses with spontaneous AF. The differences in ventricular rates between the three species as compared with the differences in body weight are small (34). The dog, human, and horse with AF may have almost equal ventricular cycles despite the fact that a horse's heart is 50 to 100 times as heavy as that of a dog. In dogs, as in humans, the ventricular rhythm is random. In horses, depending on the ventricular rate, a certain degree of periodicity may occasionally be present. This could be caused by autonomic nerve interference with AV junctional electrophysiologic properties elicited by the very long RR intervals that often occur (4 sec and longer) and are associated with a concomitant drop in blood pressure (83).



**FIG. 6.** Median RR intervals of dogs, humans, and horses with atrial fibrillation versus log body weight. For further details, see text. (From Meijler et al., ref. 34, with permission.)

## THE ATRIOVENTRICULAR NODE AS A GATEKEEPER IN ATRIAL FIBRILLATION

Patients with AF and a bypass of their AV node may experience very high ventricular rates and often ventricular fibrillation. It is fair to say that the ventricles are protected against high atrial rates like AF by the AV node (84–87). Thus the AV node may be considered as a guard or a gatekeeper, allowing some atrial impulses to pass while preventing many others from entering the gate.

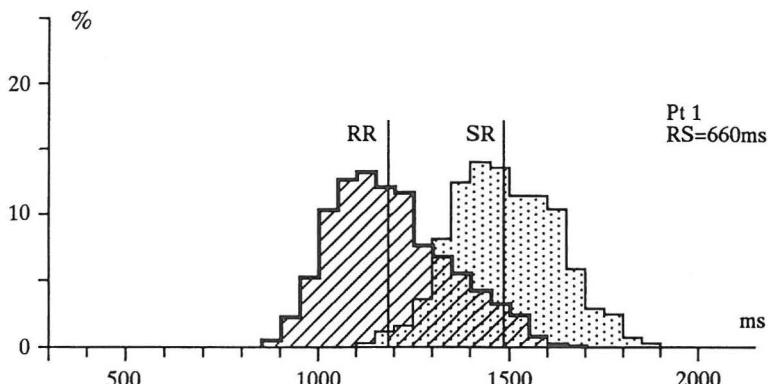
The classical theory that during AF the AV node behaves as a gatekeeper by means of decremental conduction (24,40), enabling some atrial impulses to be propagated to the ventricles, while others are prevented from propagation, has been challenged by several investigators (48,49,58,61,64,88–90). However in itself, the metaphor of the AV node as gatekeeper is useful, depending on how the function of the gatekeeper is prescribed. A gatekeeper may consider all subjects that want to pass the gate and then select, for whatever reason, one or more that will be admitted. He may also guard his gate by only letting pass subjects with certain properties, while others not having such a property are not even considered. Moreover, the gatekeeper can also set a fixed or variable time (a refractory period) within which no subject, not even one with a valid passport, is allowed to pass the gate. One may also assume that the guard changes its behavior depending on the number and quality of the impulses and the direction they come from. As we will show, the latter form of AV node behavior seems a fair description of what actually goes on.

## THE COMPENSATORY PAUSE IN ATRIAL FIBRILLATION

A compensatory pause following a premature ventricular depolarization during sinus rhythm is a well-recognized electrocardiographic phenomenon. Langendorf (91), Pritchett et al. (92), and others (93) have demonstrated that the ventricular cycle is lengthened after a ventricular extrasystole even in the presence of AF. Langendorf (91) termed this phenomenon the “compensatory pause in atrial fibrillation” and believed that it was caused by lengthening of the AV nodal refractory period due to retrograde concealed conduction into the AV node of the spontaneous or artificially induced ventricular extrasystole. However, both Moore and Spear (94) and Akhtar and coworkers (95) have subsequently shown that properly timed retrograde concealed conduction into the AV node facilitates rather than slows AV anterograde conduction. A substantial number of atrial impulses normally delayed and blocked within the AV node would be potential candidates for facilitated propagation following concealed retrograde penetration of a ventricular extrasystole into the AV node. Facilitation of anterograde transmission has to the best of our knowledge never been observed after ventricular extrasystoles in the presence of AF, nevertheless lengthening of the refractory period of the AV node by the ventricular extrasystole is not likely to explain the compensatory pause in AF.

In 1990 we postulated that the duration of the (compensatory) pause after single ventricular extrasystoles may be caused by two different mechanisms, depending on the time of the extrasystole relative to the preceding “normally propagated” QRS complex (96).

1. Relatively early, retrogradely conducted ventricular extrasystoles [interval between R wave and extrastimulus (RS in Fig. 7)] cause the histogram of the postextrasystolic RR intervals (SR in Fig. 7) to shift to the right without a change in shape when compared with the histogram of the “normal” RR intervals. Thus, a ventricular extrasys-



**FIG. 7.** Histograms of the spontaneous RR intervals (*RR*) and of the compensatory pauses (*SR*) after properly timed ventricular extrasystoles (*RS*) in a patient with atrial fibrillation. *S* stands for the ventricular extrastimulus. The similarity of both histograms should be noted. For further details, see text.

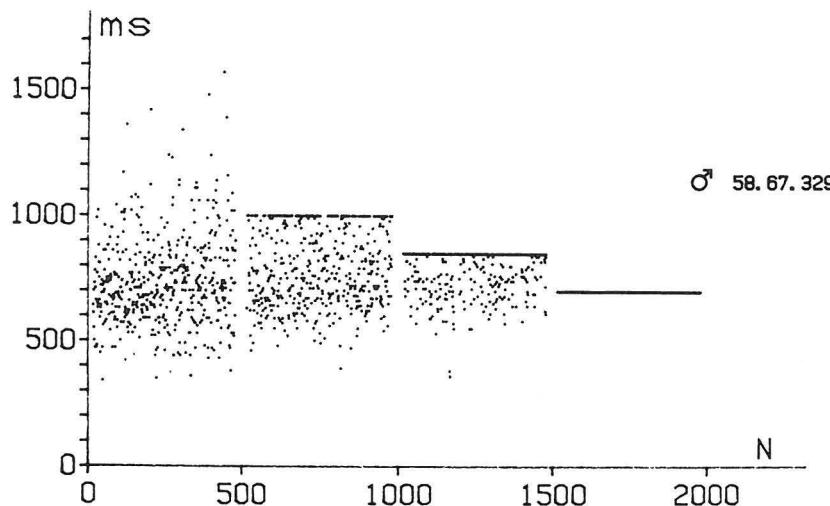
trole that reaches and depolarizes the AV node has the same effect on the timing of the next AV nodal discharge as an impulse that has depolarized the AV node from the atrial side and resets the refractory period of the AV nodal cells causing the AV nodal propagation curve to shift to the right.

2. Retrograde conduction of extrasystoles occurring later in the ventricular cycle will simply intercept anterograde impulses below the AV node, resulting in a completely different postextrasystolic histogram (96) (not shown in Fig. 7).

### THE EFFECT OF VENTRICULAR PACING IN ATRIAL FIBRILLATION

If one properly timed ventricular extrasystole penetrates into the AV node and is able to reset the AV nodal propagation curve, it follows that repeated ventricular pacing at an appropriate rate will continuously activate and reset the AV node (88,89). In Fig. 8 the effect of right ventricular (RV) pacing with decreasing pacing intervals in a patient with AF is shown in an interval plot. It can be seen that, as expected, at a pacing interval of 1,000 msec all RR intervals over 1,000 msec are abolished. However, at the same time the number of short RR intervals diminishes. This becomes even more evident at a pacing interval of 850 msec, and at 700 msec all anterograde transmission is blocked despite the fact that the pacing intervals are almost twice as long as the shortest RR intervals before ventricular pacing. *Only during AF and intact AV nodal conduction pathways is a ventricular rhythm capable of continuously blocking anterograde conduction.* In other words, during AF ventricular captures often observed during sinus rhythm and an accelerated ventricular rhythm or ventricular tachycardia should not occur. Single wide QRS complexes without a compensatory pause (91) must be due to aberrant anterograde conduction.

This observation fits well with the theory that repetitive RV pacing (or an accelerated ventricular rhythm) may cause overdrive suppression of an AV nodal pacemaker or continuously reset the AV nodal propagation curve, making it impenetrable for atrial impulses and resulting in total anterograde block. This observation can also be explained on the basis of overdrive suppression of conduction (97).



**FIG. 8.** Successive RR intervals in a patient with AF before (first 500 cycles) and during pacing on the right ventricle with a pacing interval of 1,000, 850, and 700 msec (cycles 500–2,000). At a pacing interval of 700 msec (last 500 cycles), all anterograde conduction has ceased and the rhythm has become regular. (From Wittkampf et al., ref. 89, with permission.)

#### ABSENCE OF SCALING IN ATRIAL FIBRILLATION

Another fundamental quality of the ventricular rhythm in patients with AF is the maintenance of its degree of irregularity (relative variability) or dispersion of RR intervals expressed as a constant coefficient of variation (CV) (32,33) at varying ventricular rates. This remarkable phenomenon is at odds with the principle of *scaling* (32,98), a term generally used for the linkage between atrial and ventricular rates in AF.

Schmidt-Nielsen (99) defined the term *scaling* for his studies on animal size as follows: "Scaling deals with the structural and functional consequences of changes in size or scale among otherwise similar organisms." Scaling of a rhythm cannot so simply be defined. It implies, among other things, that one can scale up or down, resulting in a higher or lower rate, respectively. The so-called scaling factor is the ratio between the number of original impulses and the number of transmitted impulses. For instance, the scaling factor in atrial flutter with a 3:1 block is 3. In this case it concerns the conversion of a (high rate) regular rhythm of the atria into another regular rhythm of the ventricles. During a regular rhythm like atrial flutter, scaling only affects the rate, while during an irregular rhythm, for example, AF, scaling would affect both rate and rhythm. Thus, in order to determine whether the AV node indeed scales down the atrial rhythm, not only the rate but also the irregularity of the atrial and ventricular rhythms have to be quantified. We therefore use the CV, which is the ratio between the standard deviation (SD) and the average cycle length (CL). Thus  $CV = SD/CL$ . It can easily be seen that at  $SD = 0$ , the CV becomes 0 as well, which implies a strictly regular rhythm. When two irregular rhythms with different rates have the same CV, their degree of irregularity or relative variability is the same. With a constant scaling factor N, the average CL of the transmitted impulses would increase by the same factor N and the CV would diminish. However, the SD will not increase by a factor N.

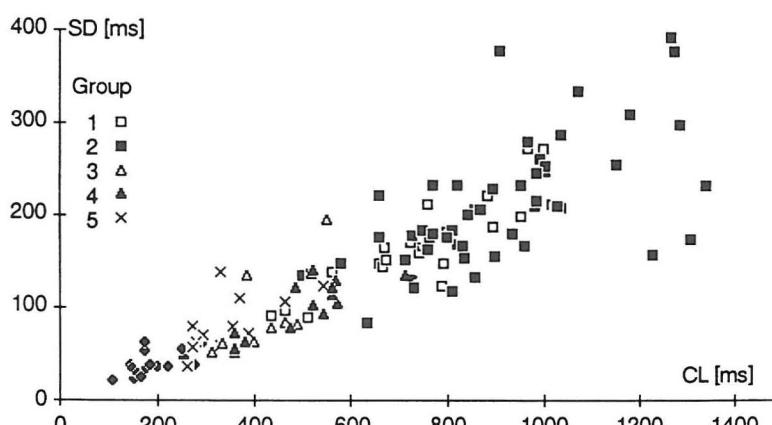
Variations in the intervals between the atrial impulses during a randomly irregular rhythm like AF will partly compensate each other, and consequently summation of N

atrial intervals would not increase the SD of the resulting average ventricular CL with a factor N, but of necessity with the square root of N (100). Therefore, in case of a scaling process as is assumed to take place during AF, the relative variability (the CV) of the scaled-down rhythm (ventricular response) must decrease when the scaling factor increases. This principle is used in the so-called atomic clock to obtain extremely stable rhythms. The greater the scaling factor, the more precise the clock. It follows that a change in rate of a rhythm without a change in its irregularity (CV) paradoxically proves that scaling has not taken place.

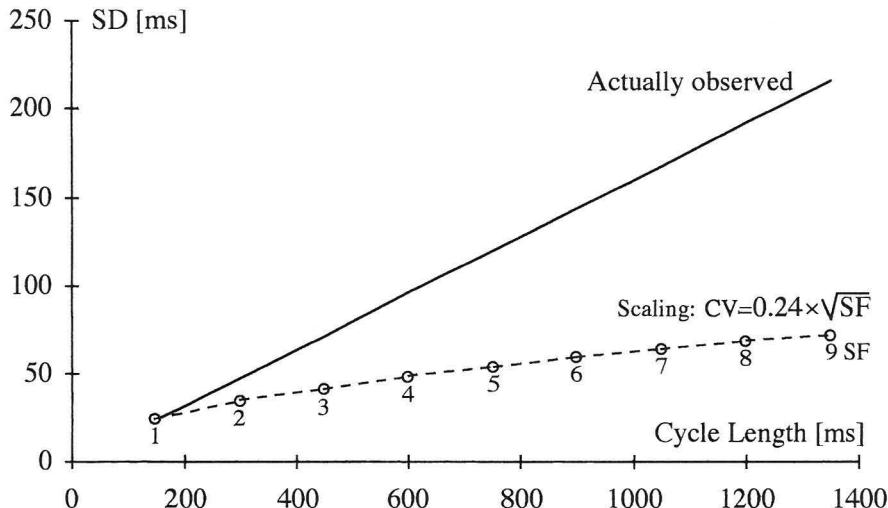
If in patients with AF scaling would take place, a greater scaling factor would result in a slower ventricular rhythm with a lesser irregularity. A slow ventricular rhythm would have to be less irregular (smaller CV) than a fast ventricular rhythm. This does not occur, as is demonstrated in Fig. 1. Despite the lower ventricular rate due to digitalis treatment, the CV remains the same. Thus digitalis only effects the rate and not the irregularity of the ventricular rhythm in AF.

Wittkampf et al. (90), including the data of Kirsh et al. (98), listed the relative variability expressed as the CV of the atrial and ventricular rhythms in 100 patients with AF under a variety of circumstances (Fig. 9) known to modulate AV nodal function and to result in rate changes of the ventricular rhythm. They found that, irrespective of the ventricular rate, the CV remained almost constant (in the order of 0.23), and thus the relative variability (degree of irregularity or dispersion of RR intervals) of all ventricular rhythms of all patients under all circumstances remained more or less the same. Again these data indicate that, in the AV node, scaling (selection of atrial impulses) does not take place. In Fig. 10 we give a schematic representation of a scaled-down rhythm compared with the actual situation.

In patients with the Wolff-Parkinson-White syndrome (WPW), AF, and transmission via the bypass tract, the ratio between SD and average CL = CV is also constant (see solid diamonds in Fig. 9, not indicated in the legend or in Table 1). Thus the degree of irregularity of the ventricular rhythm in patients with AF, irrespective of the way the atrial impulses are transmitted, is constant (Fig. 10) and seems to be an inherent property of the arrhythmia, whose source resides in the atria.



**FIG. 9.** Linear relationship between standard deviation (SD) and average cycle length (CL) of all rhythms of the five patient groups with AF shown in Table 1.



**FIG. 10.** In case of scaling the relationship between SD and CL (see Fig. 9) would follow a square root function: broken line. In real life the relationship follows a linear function: continuous line.

The preservation of relative variability of all atrial and ventricular rhythms in patients with AF strongly suggests that there is no scaling (selecting) process operative in the AV node and therefore supports the notion that decremental conduction as traditionally conceived (24,40) does not explain the slow(er) ventricular rhythm in those patients. Decremental conduction requires that an atrial impulse is selected for propagation because other blocked atrial impulses had gradually broken down the impediments for propagation. The same reasoning may be applied to the phase 4 modulation theory (58,59), because phase 4 modulation would also result in a scaling mechanism. We therefore conclude that atrial impulses are selected neither by decremental conduction (24) nor by

**TABLE 1.** Details of the five groups of patients with atrial fibrillation

Group	N	CL (msec)	SD (msec)	CV (%)
1	18	186±50	39±13	21±6
2	25	724±177	164±50	23±3
3	51	910±202	210±67	23±6
4	10	419±78	92±45	22±8
5	13	508±101	102±28	20±3
Total	117			22±5

Group 1, atrial rate and rhythm of discrete local deflections in the right atrium as recorded with an electrode catheter; group 2, ventricular rate and rhythm at rest without medication; group 3, ventricular rate and rhythm at rest with various drugs (most often digitalis); group 4, ventricular rate and rhythm during moderate exercise without medication; group 5, ventricular rate and rhythm during moderate exercise with medication.

In each of these groups of rhythms, the atrial and ventricular coefficients of variation (CV) were calculated as the ratio between the standard deviation (SD) and average cycle length (CL) of successive intervals. The outcome of the analyses is shown here and in Fig. 9.

CL, group mean of average ventricular cycle lengths; SD, group mean of standard deviations of ventricular cycle length; CV, group mean of coefficients of variation. All values are express  $\pm$  standard deviation. For further details, see text.

phase 4 modulation (58,59) but that the randomly irregular atrial electrical impulses continuously impart to cells within the AV node a similar irregular behavior. The hypothesis that random atrial impulses electrotonically modulate the AV nodal propagation curve is not at odds with the absence of scaling in AF, as is shown in our recently published computer simulation model (64).

### THE EFFECT OF DIGITALIS IN ATRIAL FIBRILLATION

Figure 1 demonstrates that digitalis can have a major effect on the ventricular rate during AF, while the ventricular rhythm remains random and the CV does not change. In this patient the mean ventricular rate decreased from 108 beats/min before digitalis, to 63 beats/min during treatment. The mean RR interval increased from 557 to 948 msec and, most importantly, the FRP of the AV node-His/Purkinje system as represented by the time between the Y axis and the beginning of the histogram increased from 350 msec (no digitalis) to 550 msec. However the decrease in mean ventricular rate is caused not only by the increase in FRP, but also, and to a major extent, by an increase of RR intervals longer than 1,000 msec.

Finally, it is of interest to note that the SD of the mean becomes considerably larger at the lower heart rate during digitalis treatment. However, as mentioned above, the ratio between SD and the mean RR interval (the CV) remains fairly constant:  $126/557 = 0.23$  versus  $233/948 = 0.24$ , indeed demonstrating that the AV node does not scale (32,90,98) and does not select the atrial impulses.

Although the effect of digitalis on ventricular rate can be blocked by atropine, as already shown by Mackenzie (8), this does not necessarily show that digitalis acts through the vagal nerve, as at that time already asserted by Sir Thomas Lewis (101). The histograms (Fig. 1) demonstrate that digitalis increases the FRP of the AV junction and that it increases the number of long RR intervals due to its direct or indirect effect on the atrial myocardium through which the number of atrial impulses increases and more electronic inhibition of AV node conduction takes place (64). Whether or not digitalis also affects other electrophysiologic properties of the AV junction cannot be stated with certainty. It may act both ways, but at the therapeutic level digitalis probably does not affect conduction velocity in the AV node-His-Purkinje system (102).

### ATRIAL FIBRILLATION IN THE WOLFF-PARKINSON-WHITE PATIENT

In the "gatekeeper" paragraph we already alluded to the significance of the Wolff-Parkinson-White (WPW) syndrome for understanding the ventricular rhythm in AF. Therefore, a single remark should be devoted to AF in patients with WPW syndrome. These patients have an aberrant connection between atrial and ventricular myocardium without AV junctional electrophysiologic properties, which short-circuits the protective function of the AV node. In the presence of AF a high ventricular rate or even ventricular fibrillation may be the result of this (103). A short refractory period and low apparent threshold will allow many more atrial impulses to reach the ventricles than in the absence of such a bypass short circuit (104).

The difference between the effect of AF on the ventricular rates in patients with and without WPW syndrome must reside in the difference of electrophysiologic properties between the Kent bundle and the AV junction. A Kent bundle transmits most of the atrial impulses, while the AV node blocks most of the atrial impulses; but in both conditions

the degree of ventricular irregularity (ventricular CV) is similar and essentially the same as the atrial CV. Both propagation systems (normal and aberrant) are confronted with the same atrial electrical activity, although almost certainly in a different spatial setting. The AV node consists of cells electrotonically modulated by the shower of atrial impulses (105) from the surrounding atrial myocardium. The Kent bundle(s) directly connect(s) the atrial and ventricular myocardium and have basically the same electrophysiologic properties as myocardium. The similarity of the irregularity of the ventricular rhythms in patients with and without WPW syndrome and AF deserves further study but is proof of the fact that it is the atrial irregularity that causes the ventricular irregularity and not some hidden property of the AV node.

### ABLATION IN ATRIAL FIBRILLATION

Ablation procedures have become a major tool in the treatment of paroxysmal AF with high ventricular rates that do not satisfactorily respond to drug treatment (106–110). A literature search showed an increase from 53 references in the period 1985 to 1990, to 77 references from 1991 till 1993, and in 1994 plus the first half of 1995, 84 references were counted.

The widespread acceptance of the concept of dual AV nodal pathways as the cause of reentrant AV nodal tachycardias requires some consideration in the light of our theory of electrotonic modulation of AV nodal propagation. Examination of available evidence regarding the presence of anatomically distinct dual AV nodal pathways does not support the notion of two anatomically distinct pathways (69). Moreover Janse et al. (111) have critically reviewed the evidence for dual AV nodal pathways. They came to the conclusion that, within the AV node, the separation between anterograde and retrograde pathways is functional and not anatomic. Support for this conclusion comes from Ho et al. (112), who studied the hearts of nine patients with electrophysiologically proven dual AV nodal pathways. They were unable to locate discrete dual pathways and concluded that “dual AV nodal pathways do not exist as a discrete entity, but rather that the AV nodal and perinodal tissues have varying and variable conduction properties.”

“Slow pathway” ablation (110) diminishes the rate of the ventricular response to AF. Apart from its effect on the refractory period an explanation could be that the “slow” pathway has an inhibitory effect on the fast pathway (113) and that by its ablation the number of atrial impulses that reach the AV node increases. The effect of slow pathway ablation in AF may thus be compared with that of digitalis, offering a viable explanation for its slowing effect on the ventricular rate. Ablation in the area of the fast pathway does not slow the ventricular response to AF and does not change the Wenckebach cycle or the refractory period of the AV node (114). The effects of ablation on ventricular rate and rhythm in AF require further study before a more definite viewpoint is possible.

### THE ROLE OF THE ATRIOVENTRICULAR NODE DURING ATRIAL FIBRILLATION

The classical theory of decremental conduction in the AV node during AF is challenged by:

1. The occurrence of a compensatory pause following properly timed ventricular extrasystoles and a shift of the postextrasystolic histogram to the right (96) and the

occurrence of complete anterograde block during RV pacing at pacing intervals of approximately twice the length of the shortest spontaneous RR previous to RV pacing (89).

2. The constancy of the CV of the ventricular rhythm at different ventricular rates (90).

Some investigators have studied the behavior of the AV node during sinus rhythm as well as during AF with mathematical modeling (59). Their studies show that during sinus rhythm the electrophysiologic behavior of the AV node can be described as an entrained biologic oscillator. We may add to this that the AV node demonstrates its pacemaker properties during atrial arrest. Moreover, the AV node shows pacemaker activity in the sense that it can be reset by ventricular extrasystoles and/or RV pacing.

We (58) and others before us (48,49) therefore postulated that in AF the AV node may behave as a pacemaker electrotonically modulated or entrained by the fibrillating atrial myocardium. This conclusion was supported by the comparison of AV nodal and SA nodal electrical function (52) and the similarity of the morphology of the two nodes (68,79,115).

Kirchhof et al. (116) showed that during induced AF the intracellular recordings from the sinus node area point to local SA conduction block and dissociated electrical activity. The same investigators (117) also found evidence that the pacemaker activity of the AV node is electrotonically depressed, thus modulated by surrounding fibrillating atrial myocardium. Outward conduction of impulses from the center of the SA node toward the atrium is practically impossible, mainly because the surrounding fibrillating atrial myocardium is refractory. The AV node, however, albeit also surrounded by fibrillating atrial myocardium, has a structural outlet, the His bundle. So impulses originating in, or passing through, the AV node and having their intervals electrotonically modulated by the electrical activity of atrial myocardium do have an outlet and can reach the His-Purkinje system.

We assume that the AV nodal propagation curve indeed is continuously electrotonically modulated by the surrounding fibrillating atrial myocardium. Jalife (118) demonstrated striking similarities between the characteristics of the sucrose gap model and those of an AV node. For instance, nonconducted impulses originating from a proximal segment can delay or advance the approach to threshold of a subsequent impulse (63).

From the available evidence we now hypothesize that during AF, atrial impulses of sufficient strength and of random timing cause continuous electrotonic modulation of the AV nodal propagation curve. Our hypothesis explains the ventricular rate and rhythm during AF and is supported by the observation that an overall high rate atrial electrical activity, such as that caused by digitalis treatment, creates more electrotonic inhibition and therefore a slower ventricular rhythm; a slow rate atrial electrical activity, such as that caused by quinidine treatment, has the opposite effect resulting in a faster ventricular rhythm.

The currently available evidence convinced us that the classical theory of decremental conduction (24,40) in the AV node cannot stand the test of the real-life situation. But decremental conduction, as well as the fairly simple and attractive model of electrotonic modulation of phase 4 of an AV nodal pacemaker equivalent (58,59), does not explain all observations, including the absence of scaling in AF, either.

Our present hypothesis is that during AF AV nodal propagation is continuously being modulated electrotonically by the atrial impulses (64). Together with the multiple wavelet hypothesis (20), it offers a credible explanation for all electrocardiographic phenomena related to or occurring during AF. It also offers a basis for the understanding of most drug

**TABLE 2.** Summary of electrocardiographic findings and derived statistics and the theories that (should) explain them.

Clinical observations	Real-life situation	Decremental conduction	Pacemaker theory	Electrotonic modulation <sup>a</sup>
Constant CV "no scaling"	+	-	-	+
Anterograde block at ventricular pacing	+	-	+	+
Resetting after VPC	+	-	+	+
Ventricular rate ↓ at atrial rate ↑	+	-	+	+

<sup>a</sup>Only finding to fulfill all criteria. See text for further details.

action and the effect of autonomic nervous control in relation to ventricular rate and rhythm in AF. It reduces the small differences between the ventricular rates in dogs, humans, and horses during AF to the well-known limited difference in electrophysiologic behavior of the respective AV nodes and the probably similar behavior of the fibrillating atria. Our findings and ideas are summarized in Table 2.

## FINAL REMARKS

In the foreword of his book *The Emperor's New Mind* (119), Roger Penrose gives a classification of theories. Theories may be superb, useful, tentative, or misguided. Our conjecture on AV nodal function during AF does not go beyond tentative, and we certainly hope it will not misguide our readers.

With respect to our dissident view of AV nodal function we may add that the advancement of science may profit from the challenge of existing and widely accepted theories. According to Popper (120) we should design (our) experiments in such a fashion that they may disprove (our own and others') theories. For the time being there are no observations that disagree with the electronic modulation of the AV nodal propagation curve theory. We realize though that the last word about AV nodal function during AF has not yet been spoken.

## CONCLUSION

During AF the AV node does not show decremental conduction. Concealed conduction can be explained on the basis of continuous electrotonic modulation of AV nodal propagation.

Ventricular rate and rhythm are dictated by:

1. The characteristics of the atrial electrical activity itself.
2. The electrotonic effect of atrial impulses on the AV nodal propagation curve.
3. The inherent electrophysiologic properties of the AV node.
4. The refractory period and threshold of the His-Purkinje system.

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