An "Account" of Digitalis and Atrial Fibrillation

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This review deals with the mechanisms by which digitalis exerts its "opium-like" action on the ventricular rate in patients with atrial fibrillation. To understand the effect of digitalis on ventricular rate and rhythm, it is essential to learn more about the basic electrophysiologic principles responsible for: 1) atrial fibrillation as such, and 2) the scaling function of the atrioventricular (AV) node-His system. It may be assumed that during atrial fibrillation, the atrial excitatory process results in randomly spaced impulses that reach the AV junction from random directions with random strength. The refractory period of and concealed conduction in the AV node enable the AV conduction system to scale down the shower of atrial impulses to a random ventricular response with a considerably lower rate.

Digitalis decreases the ventricular rate through two synergistic pharmacologic actions: 1) digitalis increases the refractory period of the AV node, and 2) digitalis decreases the refractory period of the atrial myocardium through a direct and indirect effect (vagotonic and vagomimetic). A decrease in the refractory period of the atrial myocardium results in more atrial impulses reaching the AV junction in a given unit of time. More atrial impulses result in a greater degree of concealed conduction in the AV node and, thus, in a slower ventricular rate. The ventricular rhythm remains random during digitalis treatment. Digitalis is the only drug that effects an increase in the refractory period of and concealed conduction within the AV node. Two hundred years after its discovery, digitalis remains the drug of choice for the treatment of patients with sustained atrial fibrillation.

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Digitalis is not only one of the oldest drugs still in abundant use in present day medicine, it is also one of the most studied and described (1–7). The number of published reports on digitalis is so overwhelming that any list of references is more or less arbitrary, exhibiting the author's preferences or library. It is of great interest that this herb extracted from the leaves of an elegant although not too colorful plant still keeps our minds and textbook writers busy.

Attempting to shed some light on digitalis and atrial fibrillation is in some ways, similar to trying to solve one equation with two unknowns. Two hundred years after its discovery, the action of digitalis in atrial fibrillation is not fully understood and its interpretation is "subject to contention still" (8).

Historical Background

About 100 years ago, Mackenzie (9) started his studies on heart irregularities, but to this very day, the pathophysiologic mechanisms that cause atrial fibrillation have not been fully understood and the nature of the ventricular ir-

regularity is still not without controversy (10). At the crossroads of a drug that is 200 years old and a cardiac arrhythmia that has been recognized for approximately 100 years, we can only humbly confess that Mackenzie's words of 75 years ago still hold: ". . . everyone who has carefully studied the description usually given of the effects of digitalis on the human heart, cannot but be struck with the absence of agreement among the different writers. . ." (11). However, concerning the effect of digitalis itself, Mackenzie is less insecure: ". . . with only rare exceptions, all the cases that showed a marked effect [of digitalis] upon the heart were cases with auricular fibrillation" (11). This beneficial effect was probably clearly formulated for the first time by Bouillaud in 1836: "De tous les sédatifs auxquels on puisse recourir, le plus efficace, le plus direct, c'est incontestablement la digitale: ce médicament, comme je l'ai déjà dit, est la véritable opium du coeur" (12). This was nearly 70 years before Hering (13) distinguished the pulsus irregularis perpetuus from other cardiac irregularities, but he did not recognize the disappearance of all signs of atrial activity. Mackenzie had noted that when a patient with mitral stenosis developed atrial fibrillation, the A wave of the jugular vein and the presystolic murmur disappeared (11). Before the appearance of the electrocardiographic description of atrial fibrillation by Lewis (14) and Rothberger and Winterberg (15), Mackenzie actually spoke of "atrial paralysis" (11).

According to McMichael (8), Bouillaud gave ". . . a vivid description of a patient with severe mitral stenosis and delirium cordis where the rapid, irregular pulse was slowed dramatically by digitalis, though it remained irregular." Denolin (16) in his essay, "Linking Withering to the Present," also quotes Bouillaud: ". . . la digitale, veritable opium du coeur." "Digitalis, opium for the heart," may be the best way to summarize the action of digitalis in atrial fibrillation.

Among the many patients Withering studied, he noticed a number in whom the action of the heart became slower during treatment with "foxglove." "On the basis of Withering's description of the patients he treated, it has been assumed that some of his patients suffered from auricular fibrillation" (17). One may add that if that had not been the case, the beneficial effect of digitalis in patients with "dropsy" would probably not have been discovered, and certainly not at that time.
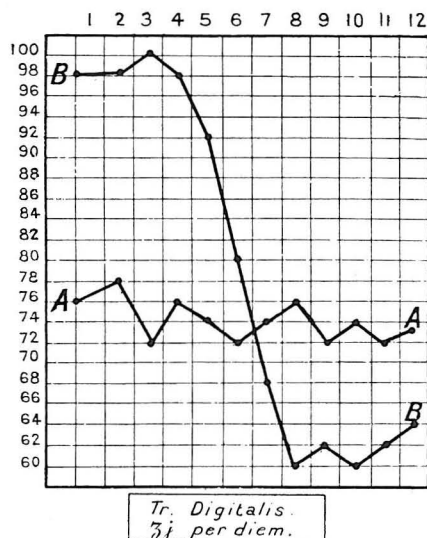
It was again Mackenzie (11) who beautifully demonstrated that in patients with mitral stenosis, the same doses of digitalis "had little or no effect on the heart rate in the patients with the normal rhythm (A), while there was a rapid decrease in the rate in the patients with auricular fibrillation (B)" (Fig. 1).

It is of more than historical interest to recall the discussion between Mackenzie and Thomas Lewis (8) on the mechanism of the action of digitalis in atrial fibrillation. Mackenzie had shown that administration of atropine, after slowing of the pulse by digitalis, accelerated the heart rate to its original level, and he concluded that the initial effect of digitalis was thus exerted through the vagus nerve. This point of view is still accepted (18) and is expressed in recent monographs and textbooks. Lewis, however, objected to Mackenzie's interpretation (8), saying that after digitalis, atropine should not merely bring the heart rate to the original level, but should accelerate it to a rate higher than before digitalis was administrated (Fig. 2). Although Lewis's interpretation of the effect of atropine in patients with atrial fibrillation and digitalis was rejected by McMichael (8), Lewis may have had a valid point. Digitalis has a direct effect on isolated atrial myocardium (19–21), and it is difficult to believe that this direct effect would not be present in the intact organism. In patients who have undergone cardiac transplantation and whose heart is thus denervated, long-term administration of digitalis also exerts a direct AV nodal effect to increase both effective and functional refractory periods (22).

In the course of the 200 years that digitalis has been used in medicine, its slowing effect on the ventricular rate in patients with atrial fibrillation has been well established. It seems fair to assume that digitalis exerts its action of decreasing ventricular rate directly and indirectly by means of vagal stimulation (23,24). This report deals with the pattern of the ventricular rhythm during atrial fibrillation and with the basic electrophysiologic mechanisms that may explain the "opium effect" of digitalis on the heart.
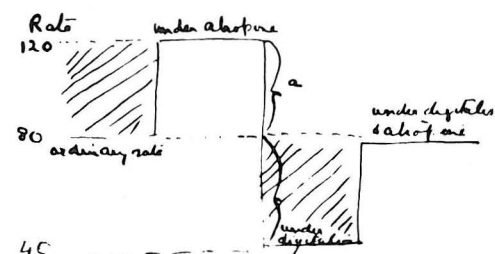
Figure 1. Effect of digitalis on heart rate during sinus rhythm (A) and atrial fibrillation (B). (Reproduced from Mackenzie J [11].)

Figure 2. Drawing by Lewis of his interpretation of the action of atropine on heart rate in a digitalized patient with atrial fibrillation. (Reproduced from McMichael J [8] with the permission of the author and the Wellcome Institute, London.)

Ventricular Rhythm in Atrial Fibrillation

The most striking clinical feature of atrial fibrillation is the total irregularity of the heartbeat (13). With the introduction of the digital computer in the early 1960s, it became possible to describe the irregular ventricular rhythm in atrial fibrillation in more precise terms (25). In 1970, we (26) demonstrated that in human patients the ventricular response in atrial fibrillation is random, irrespective of whether the patient is or is not given digitalis or is at rest or being exercised.

A random series of events is marked by an absence of bias and a lack of predictable incidence (27). The best example of a random process in time is the emission of photons by radioactive material. For the ventricular rhythm in atrial fibrillation, it means that there is no interrelation between the duration of successive RR intervals. The duration of any forthcoming RR interval cannot be predicted. If the ventricular rhythm in human patients with atrial fibrillation in the absence of advanced or complete AV block has nonrandom episodes, it can be assumed that the rhythm contains or is interrupted by nodal or ventricular extrasystoles or tachycardias (28).

Ventricular rhythm analysis. There are several ways to define a series of events in quantitative terms. One method is to use histograms and serial autocorrelograms showing the duration of the intervals between the events. The histogram of the ventricular rhythm in atrial fibrillation reveals the average rate of the R waves and the distribution of the RR interval durations. Serial autocorrelograms provide information about the presence or absence of a relation between all recorded RR intervals. Histograms and serial autocorrelograms are obtained from a large number of successive RR intervals. The larger the number of RR intervals used for these computations the more accurate the results. We usually employ several hundred to 1,000 RR intervals representing an electrocardiographic recording time between 15 and 30 minutes. By means of analog to digital conversion of the recorded electrocardiographic signal (usually lead II or another lead with a prominent R wave), the duration of all RR intervals is measured. The RR interval durations are arranged in successive order, for instance, 1 to 500. It is now possible to correlate *each* RR interval duration with itself, with the duration of the next RR interval or with an RR interval duration that is 10 or 20 intervals ahead. A correlation coefficient zero is the result of correlating the duration of each RR interval with itself, and it follows that it must equal $+1$. 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 the two sets of RR interval durations. The kth correlation coefficient is a measure of the relation between all RR intervals that are k intervals apart. Correlation coefficients lack dimension. In a stationary random process, all correlation coefficients greater than zero have values that are statistically not different from zero. The opposite is also true; if in a serial autocorrelogram the values of successive correlation coefficients of the RR interval durations beyond correlation coefficient zero do not differ from zero, that rhythm may be called random. In summary, the ventricular rhythm of patients with atrial fibrillation is characterized by its histogram and serial autocorrelogram.

Rhythm analysis obtained in this manner and presented in this fashion may teach us more about the following questions. 1) What abnormal conditions affecting the basic electrophysiologic state of the atria are responsible for the inception and perpetuation of atrial fibrillation? 2) What factors govern the response of the AV transmission system and the ventricles to the shower of impulses arriving from above? These two questions were formulated by Brody in 1970 (25). We may add a third question: How are the basic electrophysiologic state of the atria and the response of the AV conduction system to the atrial impulses affected by digitalis during atrial fibrillation?

Examples of data from patients. Figure 3 demonstrates the histogram and serial autocorrelogram of the ventricular rhythm of a patient with atrial fibrillation before and after digitalis treatment. This figure has been chosen for two reasons. First, it represents our earliest observations on this subject (26). Second, and more important, it represents the effect of digitalis on the ventricular rhythm during atrial fibrillation in a nearly ideal way. It can be seen that the serial autocorrelogram does not change during digitalis treatment. With the exception of correlation coefficient zero, which by definition equals $+1$, all further coefficients do not differ from zero. In other words, whether this patient with atrial fibrillation is or is not taking digitalis, the ventricular rhythm is completely random.

The histograms, however, are quite different and reveal the effect of digitalis. The histograms before and during digitalis administration demonstrate that the mean ventricular rate decreases from 108 beats/min in the untreated patient to 63 beats/min during treatment. The mean RR interval increases from 557 to 948 ms and, most importantly, the functional refractory period of the AV node-His system, as represented by the time between the Y axis and the beginning of the histogram (29,30), increases from 350 ms in Figure 3A (no digitalis) to 550 ms in Figure 3B (during digitalis administration). At the same time, it can be observed that the decrease in the mean ventricular rate is due not only to the increase in the functional refractory period, but also and to a major extent to the occurrence of a considerable number of RR intervals longer than 1,000 ms. Finally, it is of interest to note that the so-called dispersion (31) or coefficient of variation (32) of the RR intervals, which in Figure 3 is illustrated by the standard deviation of the mean, becomes considerably larger at the lower heart rate during digitalis treatment.
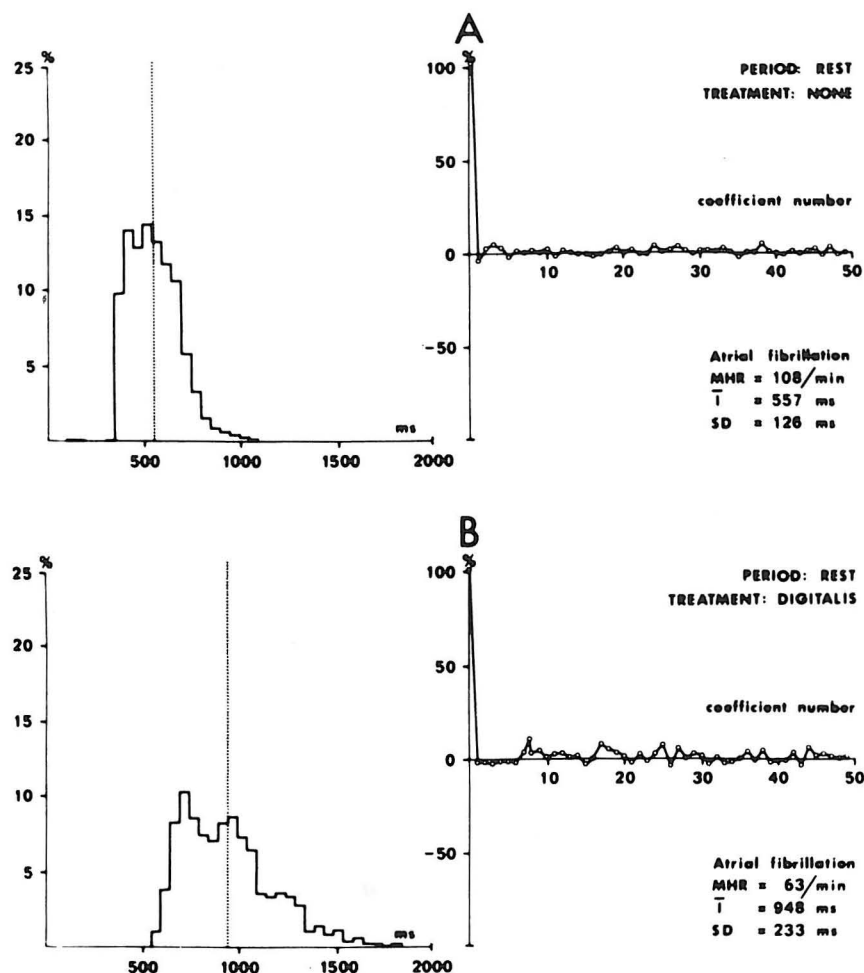
Figure 3. Histogram **(left)** and serial autocorrelogram **(right)** before **(A)** and during **(B)** digitalis treatment. For further details, see text. (Reproduced from Bootsma BK, et al. [26] with permission of the American Heart Association, Inc.)

In Figure 4, the effect of digitalis on ventricular rate and rhythm is demonstrated in a different manner and in a different patient. The duration of each RR interval has been plotted against its sequential RR interval number. In the untreated patient (Fig. 4A), the lower limit of RR interval duration is around the 400 ms line; only a few RR intervals are longer than 1,200 ms. In the same patient during digitalis treatment (Fig. 4B), this lower limit increases to about 600 ms with only a few shorter RR intervals, while several are longer than 1,400 ms. Needless to say the serial autocorrelograms before and during the administration of digitalis remained the same.
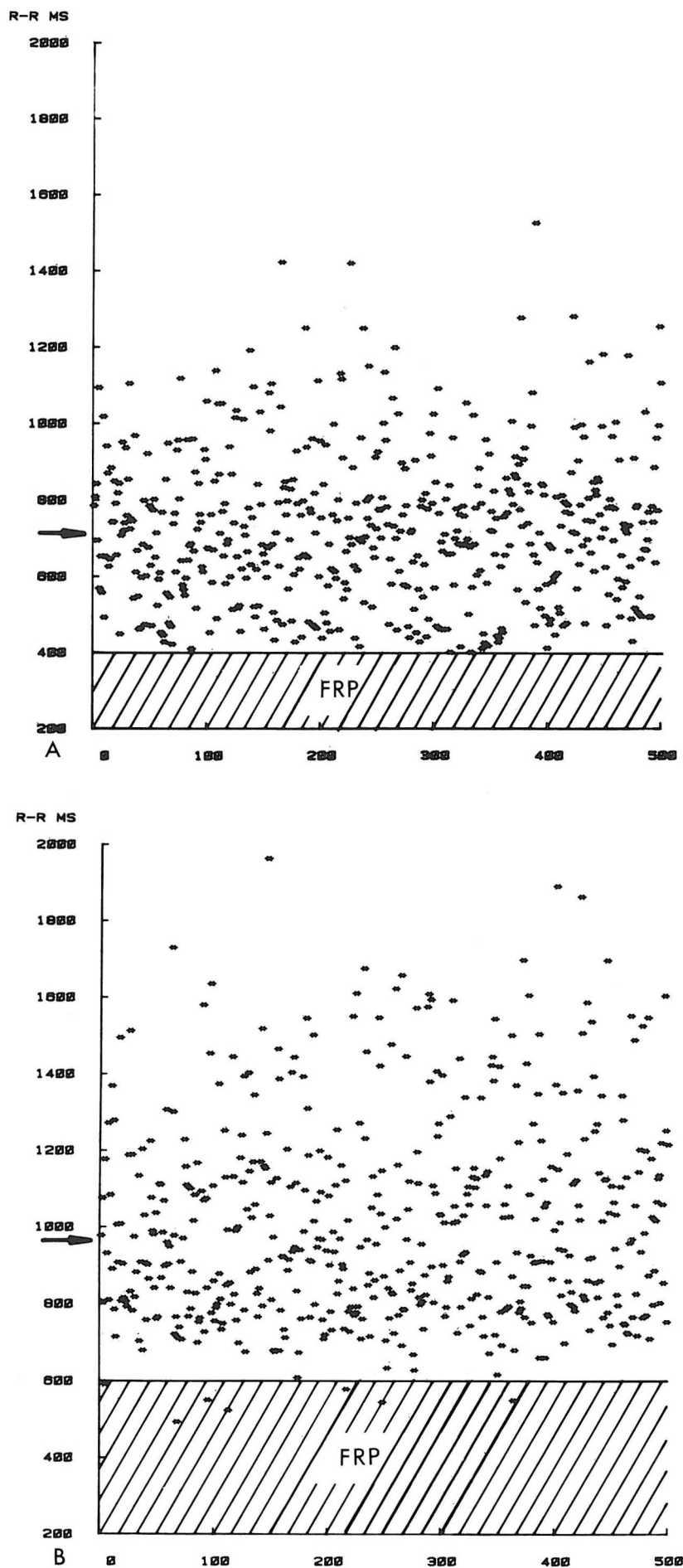
The results obtained in these two patients exemplify our observations in numerous patients and dogs with atrial fibrillation whom we have studied in the last 15 years. Dogs with spontaneous atrial fibrillation, whether or not they are receiving digitalis, also have a random ventricular rhythm (33). Digitalis always increases the functional refractory period and decreases the mean heart rate. There is a predictable increase in the number and duration of long RR intervals and the coefficient of variation of RR interval durations.

Basic Electrophysiologic State of the Atria During Atrial Fibrillation

The ventricular rhythm in atrial fibrillation reflects the atrial impulses that traverse the AV node-His system. The intervals between those atrial impulses that reach the ventricular myocardium must, therefore, show a random pattern. It is difficult to conceive of an organized or patterned atrial excitation process that ultimately produces randomly spaced atrial impulses. We therefore concluded or at least postulated that the atrial impulses reach the AV node from random directions with random strength and in a random sequence (26,34). Hoffman and Bigger (23) offer support for this hypothesis by stating that ". . . in typical atrial fibrillation the impulse spreads through the atrial syncytium in a manner that may best be described as random reentry." The impulses arriving at the AV node as a result of this atrial activity are numerous (as many as 500/min) and random.

The hypothesis of random atrial excitation in atrial fibrillation finds further support in the observation that signal analysis of the bipolar right atrial electrogram reveals that the signal has noiselike characteristics (35). Puech et al.

Figure 4. RR interval duration versus RR interval sequence number in a patient with atrial fibrillation before (**A**) and during (**B**) digitalis treatment. The **shaded area** represents the functional refractory period (FRP) of the AV conduction system. The **arrow** points to the median RR interval duration. For further details, see text.

(36), using intraatrial mapping during atrial fibrillation, found that the atrial electrogram shows chaotic local activity, completely disorganized and without isoelectric intervals. Locally obtained atrial electrograms may not, however, be representative of the activity of the entire atrial myocardium. On the other hand, the finding by Battersby (37) of a periodic component in the atrial waveform during atrial fibrillation may be due to the fact that he analyzed atrial activity on the surface electrocardiogram, which may have introduced an averaging error. However, both the interval between the atrial impulses as well as their strength and direction vary continuously (38,39) and may, thus, cause or contribute to a random pattern of atrial excitation that ultimately reaches the ventricles. In any case, the random reentry or random wavelet hypothesis of atrial excitation in atrial fibrillation is in agreement with the findings of Moe and Abildskov (40) and Sano and Scher (41) and offers a firm background for the random pattern of the ventricular rhythm. The question remains why the AV node-His system cannot impose order on the random sequence of the conducted atrial impulses.

Role of the AV Node-His System During Atrial Fibrillation

His bundle recordings during atrial fibrillation show the spikes of the atrial impulses that have traversed the AV node (42). These are only a fraction of the impulses that reach the AV junction.

Concealed conduction. The explanation of the Ashman phenomenon in clinical electrocardiography is based on the notion that the refractory period of the His-Purkinje system is related directionally to the length of the preceding cycle (43,44). The refractory period lengthens after a long preceding cycle and shortens after a short cycle. The same principle may be applicable for the AV node itself. Concealed conduction (45–49) may impede AV conduction for a considerable time and, thus, increase RR interval duration by extending the refractory period of the AV node-His system. However, immediately after a conducted impulse, the refractory period of the AV node can only be dictated by the duration of the interval between the two preceding atrial impulses that have actually reached the His-Purkinje system.

AV nodal memory. For that reason, it seems justified to extrapolate from the changes in AV conduction time during a variety of well defined atrial rhythms induced in human beings, dogs and rats (50–53) to AV nodal behavior during atrial fibrillation. It was found that adaptation of AV conduction time to stepwise atrial rate changes depends on time rather than on the number of cardiac cycles (50,54). Those atrial-induced changes in AV conduction time show a short time constant or memory, memory being the time the AV conduction system needs to adapt to changes in intervals between atrial impulses. The AV nodal memory appears to be independent of the degree of the atrial rate

change. In human beings, AV nodal memory may last between 1.5 and 2 seconds after an increase in atrial rate (50). After a decrease in atrial rate, the AV nodal memory was always shorter than the duration between two conducted atrial impulses. In other words, the AV node "forgets" its own conduction history in 1.5 seconds when the interval between conducted atrial impulses shortens. When the interval between atrial impulses increases, the AV nodal memory is even shorter and cannot be measured. This resembles the physical mechanism called "hysteresis." It follows that during atrial fibrillation with constantly changing durations of intervals between conducted atrial impulses, AV nodal memory is in general too short to affect the random sequence of the conducted atrial impulses.

Baroreflex feedback effect on AV conduction. In horses with atrial fibrillation, RR intervals of 3 to 5 seconds are quite common. This causes a considerable decrease in blood pressure and a baroreflex feedback effect on AV conduction (55) resulting in a periodicity in the serial autocorrelogram. When the administration of atropine or quinidine caused the long RR intervals to disappear, the periodicity in the serial autocorrelogram also disappeared and the ventricular rhythm became fully random similar to that in human patients and dogs. In human patients with atrial fibrillation, RR intervals of longer than 2 seconds are rare and, therefore, large decreases in blood pressure do not occur. Moreover, the latency for the baroreceptor reflex response in human beings is relatively long (56,57) and too slow to interfere with AV conduction. A long-term effect of the autonomic nervous system (for instance, during exercise or beta-adrenergic blockade) on the ventricular rate in atrial fibrillation may, of course, be present (58). In human patients, this long-term effect does not interfere with the random pattern of the ventricular rhythm during atrial fibrillation, but may increase or decrease ventricular rate.

Thus, for two reasons the AV node-His system seems unable to interfere with the random sequence of conducted atrial impulses: 1) its time constant or memory is too short to alter significantly the interval between conducted atrial impulses, and 2) the baroreceptor feedback mechanism is too insensitive and too slow to affect AV conduction on a beat to beat basis.

Effect of Digitalis on AV Conduction and Atrial Excitation During Atrial Fibrillation

The refractory period of and concealed conduction within the AV node are the accepted mechanisms responsible for slowing the ventricular rate in relation to the atrial rate during atrial fibrillation (59–61).

Increased refractory period of the AV node. The refractory period of the AV conduction system sets the lower limits of RR interval duration in atrial fibrillation. No atrial impulse is able to reach the ventricles at an interval shorter than the refractory period of the AV node-His system. Dig-

italis increases the duration of the refractory period of the AV conduction system (18,62).

However, the effect of digitalis on the AV conduction system proper only partly explains the "opium effect" of digitalis on the ventricular rate in patients with atrial fibrillation. This is clearly demonstrated in the histograms of Figure 3 and the scatter plots of Figure 4. The major effect of digitalis on the ventricular rate is seen to be the increase in number and duration of long RR intervals. Although the duration of the refractory period of the AV node increases during digitalis treatment, this in itself cannot explain the occurrence of RR intervals of 1.5 seconds or longer; similarly, the refractory period of the normal human AV node-His system during digitalis treatment seldomly exceeds 600 ms. To determine the major opium effect of digitalis, we must look outside the AV node-His system (26).

Shortened refractory period of atrial myocardium. The effect of digitalis on the electrophysiologic properties of the atrial myocardium, whether totally, partly or not at all mediated through the vagal nerve, can explain why digitalis slows the ventricular rate in atrial fibrillation. Digitalis decreases the refractory period of the atrial myocardium (18,19) and, in this aspect, it simulates the effect of vagal stimulation (63). It is likely, especially because atropine can reverse the opium effect of digitalis (8), that part of the digitalis action is through a vagal effect. Digitalis probably has a twofold action: it affects the atrial myocardium both directly and by its vagal action (63).

Shortening the refractory period of the atrial myocardium will increase the number of atrial impulses that reach the AV junction in a given unit of time. This increased number of impulses will increase concealed conduction in the AV node and, thus, fewer atrial impulses will reach the ventricles (61). The paradox that a higher atrial rate establishes a lower ventricular rate, based on concealed conduction in the AV node, is a safeguard that protects the ventricles against excessively high rates or progression to ventricular fibrillation as a result of atrial fibrillation; this is also the key to the opium effect of digitalis (42,64,65). In isolated rat hearts, concealed conduction in the AV node can indeed be controlled and quantified by manipulating the rate and rhythm of the atria (66).

The protective function of the AV node in the presence of the increased number of fibrillation waves due to digitalis is illustrated in patients with the Wolff-Parkinson-White syndrome (35). The shorter refractory period of the accessory pathway is not necessarily the culprit that causes high ventricular rates or even ventricular fibrillation. It is the lack of or diminished capacity for concealed conduction in the accessory pathway that threatens such patients (Table 1). (67).

Atrial rate, AV nodal size and ventricular rate. The normal AV node acts as a Cerberus between the atria and the ventricles, a Cerberus whose capacity for protection increases with the intensity of the threat. We may assume

Table 1. Effects of Digitalis in Patients With Wolff-Parkinson-White Syndrome and Atrial Fibrillation

Effects
  1. Shorter refractory period of atrial myocardium
  2. Higher atrial excitation rate
  3. Shorter refractory period of the bypass tract
  4. Longer refractory period of AV node-His system
  5. Shorter refractory period of ventricular myocardium
Consequences
  1. Preference for bypass tract conduction
  2. Increased ventricular pre-excitation
  3. Concealed conduction, if present, not increased
  4. Higher ventricular rate
  5. Promotion of ventricular fibrillation

that the capacity for concealed conduction in the AV node is also related to the number of cells and their electrical nonuniformity (68–72). The increase in concealment in the AV conduction system by digitalis may, at least in part, also be due to increasing electrical nonuniformity in the AV node. Comparative studies of atrial fibrillation in dogs, human patients and horses have shown that with the increase in size of the heart and the AV node, the median RR interval increases and average ventricular rate decreases especially because of more RR intervals of longer duration (32). Since cell size (myocardial and other) is more or less constant in all mammals (73–75), the AV node of a horse must contain more cells than that of a human being, which may explain the occurrence of the longer RR intervals. Thus, there is a trade-off between atrial rate, AV nodal size and function and ventricular rate during atrial fibrillation.

Digitalis: Drug of Choice in Atrial Fibrillation

Although this review does not answer all of Brody's questions (25), I believe that it comes close. Our present knowledge of the electrophysiologic properties of the atrial myocardium and the AV node-His system and the work of Moe et al. (76,77) and Alessie et al. (78) provide a fair insight into, to use Brody's terms again, the "inception" and "perpetuation" of atrial fibrillation (25). It is of special interest that by its action on the atrial myocardium, digitalis promotes the initiation and perpetuation of atrial fibrillation. We are closer to understanding the factors that govern the response of the AV transmission (or should we say nontransmission?) system to the shower of impulses arriving from above and the effect of digitalis on atrial excitation and AV conduction. The efficacy of the AV node for blocking atrial impulses increases with the number of impulses that reach the AV junction. Digitalis exerts its opium effect to a large extent by increasing the rate of atrial impulse formation. The unique two-sided effect of digitalis, on 1) the AV node, and 2) the atrial myocardium, makes it the drug of choice for the treatment of patients with sustained atrial fibrillation.

The statement made by Sir Thomas Lewis in 1912 is equally pertinent today (79). He said: "In brief, the original rapidity of the pulse and its irregularity, the character of the irregularity, the loss of the auricular wave in the neck, the loss of the P summit in the electro-cardiogram, the loss of presystolic murmur, the presence of rapid oscillations in the venous curve, the presence of oscillations in the electro-cardiogram, the varying rate of the ventricle in a single patient or from patient to patient, the action of digitalis—each and all are clear once the true explanation of the mechanism is grasped. And this explanation, as I have shown you, is that in such case we have to deal with fibrillating auricles."

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