Atrial Fibrillation: The Blind Man's Elephant

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This paper seeks to explain that most puzzling of all the forms of irregularity of the heart, where the heart is never regular in its action, where seldom or never two beats of the same character follow one another.

This is the opening sentence of Mackenzie's paper in 1904 in the *British Medical Journal*[1] in which he described an arrhythmia of the heart that we call "atrial fibrillation" today.

Definition

Atrial fibrillation has been defined by a WHO/ISC Task Force 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)."[2] This is an electrocardiographic description that is quite useful for routine, daily clinical practice, but which has limited meaning for understanding the mechanism(s) involved. When one takes a closer look at the above-mentioned definition, one notices that the electrocardiographic diagnosis of atrial fibrillation requires a number of anatomical and functional conditions. The anatomical components of the definition are: the atria, the atrioventricular (AV) node, and the ventricles. The functional components are: atrial electrical behavior, AV nodal function, and the ventricular response.

Diagnosis

The clinical picture of atrial fibrillation consists of a number of separate entities, and each student of this frequently occurring arrhythmia will have to take this into account. Emphasis may be put on one of the anatomical and/or physiological ingredients of the definition. In the clinical setting of atrial fibrillation the ventricular response must be random[2] to conclude that the atria are fibrillating. To the naked eye, the differential diagnosis between atrial flutter and atrial fibrillation may be quite difficult[3] and to be certain, a mathematical analysis of the ventricular response would be desirable. A random ventricular rhythm requires normal AV nodal/junctional function, whether one accepts concealed conduction[4,5] as the mechanism that scales the atrial impulses or believes that electrotonic modulation of an AV nodal pacemaker protects the ventricles against the high rate of the fibrillating atria.[6]

Since atrial fibrillation has many facets to be considered, looking at only one of them may lead to the "blind man's elephant syndrome." One may actually reach conclusions that, once the whole animal is seen, will not meet the test of the real-life situation. We will consider each component of atrial fibrillation separately, ultimately trying to come up with a picture of the whole elephant.

Clinical Relevance

The clinical and social relevance of atrial fibrillation surpasses all other arrhythmias. Selzer[7] called atrial fibrillation "the grandfather of all cardiac arrhythmias," an expression that may be paraphrased by stating that atrial fibrillation is the cardiac arrhythmia of grandfathers and grandmothers, since it is a frequent finding in old age. More than 50% of 1,212 patients in Godtfredsen's series with atrial fibrillation[8] were over 70 years of age. Moreover, it is a well-known
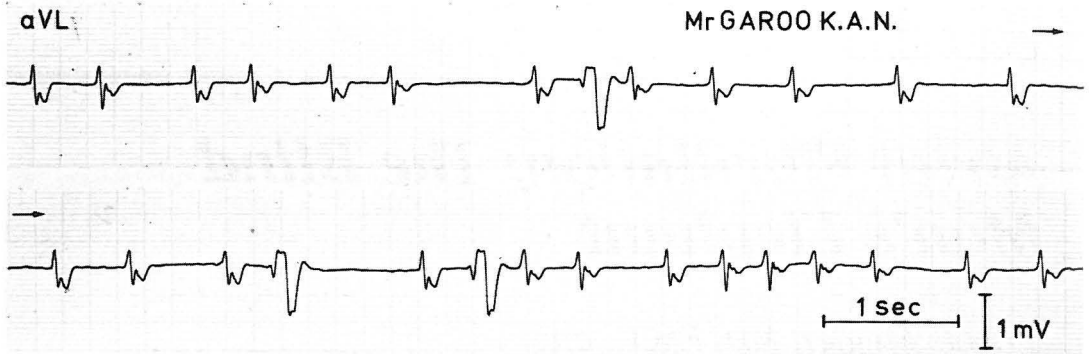
FIGURE 15.1 Atrial fibrillation in a kangaroo—the Ashman phenomenon.[117]

complication of mitral valvular disease, hyperthyroidism, and coronary artery disease.[8–11] It is frequently seen in the intensive care units, especially after cardiac surgery.[12] There is sustained atrial fibrillation, paroxysmal atrial fibrillation, and lone atrial fibrillation; all have in common a random ventricular response. However, in case of atrial fibrillation and complete AV block or a ventricular tachycardia, the ventricular rhythm may be regular, at least not randomly irregular, while the atria fibrillate. Atrial fibrillation occurs not only in humans but in large dogs (over 20 kg),[13] and horses.[14–16] We have observed one case in a kangaroo (Fig. 15.1), and have been looking for it in elephants[17] and whales.[18]

HISTORICAL REMARKS

In 1850, Hoffa and Ludwig[19] described atrial fibrillation in an animal experiment. What is called atrial fibrillation in patients today was discovered as "pulsus irregularis perpetuus" by Hering in 1903,[20] although Scherf and Schott[21] mention the discovery of atrial fibrillation by Vulpian in 1874. Mackenzie in his paper in 1904[1] did not link "the cause of continuous irregularity of the heart" to atrial or auricular fibrillation, as it was called at the beginning of our century.

> The history of the recognition of fibrillation of the auricles will impress you with the dimness of our eyes and the opacity of the obstacles which embarrass our vision. You will know how blind we have been to things which once seen, are so apparent.

This statement by Sir Thomas Lewis in 1912[22] is no less appropriate than the opening sentence of Mackenzie's article in 1904.[1] Mackenzie originally attributed the continuous irreg-

ularity of the heart to what he called a "nodal rhythm" because of the absence of a wave in the jugular pulse. He still may have been right, albeit for the wrong reasons, as will be explained later. Five years later, Lewis produced evidence that the irregularity of the heart probably results from fibrillation of the auricles, but this was after the introduction of the electrocardiograph.[23] Final proof had to wait until 1912, when Lewis observed that horses with complete irregularity of the heart had chronic fibrillation of the auricles.[24] After this, atrial fibrillation was established as an important and frequently occurring arrhythmia.[25,26] If Mackenzie, like Lewis,[22] had used the electrocardiograph, he would have recognized that during atrial fibrillation there is no atrial arrest as seems to be the case when we observe only the jugular pulse.

THE ROLE OF THE ATRIA IN ATRIAL FIBRILLATION

The random pattern of the ventricular response during atrial fibrillation points to an electrical behavior of the atria that almost certainly is random[27,28] because whatever the mechanism in the AV node that reduces the fast atrial rate to a much slower ventricular rate, it is unlikely that the AV node would be able to transform a nonrandom atrial input into a random ventricular response. Moreover, we and others have shown that in patients with atrial fibrillation who have Wolff-Parkinson-White syndrome and conduction through the bypass the ventricular rhythm is also random.[28,29] Thus, it seems fair to conclude that the cause of atrial fibrillation is an erratic electrical behavior of the atrial myocardium, resulting in a random sequence of atrial impulses of varying amplitude, which reach the AV node from random directions.[30,31]

Electrical Inhomogeneity

Garrey[32] in 1914 probably was the first to relate the nature of fibrillatory contractions of the heart to tissue mass and form. A solid basis for our understanding of (especially atrial) fibrillation has been provided by Moe and his colleagues.[33–35] Using computer simulation, they analyzed and defined the factors that cause the transition of the organized pattern of normal atrial excitation into self-sustaining, chaotic electrical behavior of the fibrillating atria. Moe and coworkers discovered that fibrillatory activity depends on (a) the total number of cells involved and (b) the electrical properties of those cells.

The large number of cells and unstable electrical properties (inhomogeneity) control the excitation process of the atria. Large atria will fibrillate much easier than small atria with a smaller number of cells and with the same or similar cellular electrical properties.

The Atrial Electrogram

Puech et al.[36] and others[27–29] have attempted to study the electrical activity of the atria in patients with atrial fibrillation. Using electrode-catheters, they recorded uni- and bipolar electrograms from different sites in the fibrillating atria and concluded from the appearance of the recorded electrograms the presence of atrial fibrillation. They also observed that in different patients atrial fibrillation may look different, while in one patient different atrial electrograms were recorded from different sites in the right atrium. We performed signal analysis of the atrial electrogram to learn more about the electrical behavior of the atria in patients with atrial fibrillation.[28] Analysis of the intervals between the zero crossings of the electrical signal by means of autocorrelograms showed absence of correlation between successive intervals. In other words, the atrial rhythm, assuming that the zero crossing method delivers a rhythm that reliably represents the rhythm of the fibrillating atria, is random with a rate between 300 and 600 episodes per minute.[28,36–38] However, not only the sequence of the recorded signals displays the erratic electrical behavior of the fibrillating atria, but also the shape and the amplitude of the signals do not seem to show any repetition either.

Unipolar electrograms do not reveal information about the direction(s) of atrial excitation during fibrillation. Bipolar recordings show continuously changing patterns of atrial excitation, which implies that there is no organized spread of excitation in the atria as observed during sinus or any other atrial rhythm.[39] Signal analysis of ventricular electrograms and electrocardiograms during ventricular fibrillation has demonstrated local areas of electrical activity that give an illusion of wave fronts traveling from one site to another.[40] We may assume that also during atrial fibrillation local areas of electrical activity are present. The work of Allessie and his group[41,42] has produced further evidence that multiple so-called wandering wavelets are the basis of atrial fibrillation. However, as clearly demonstrated,[43] experimentally induced atrial fibrillation may not be representative of sustained atrial fibrillation in humans, dogs, and horses.

We recapitulate the electrical behavior of the atria during atrial fibrillation, as follows[44]: (a) The rhythm at any site of the atria is random with a rate of approximately 300 to 600/min. (b) The electrical activity is restricted to more or less defined areas—in other words, there is no spread of activation. (c) The recorded signals vary continuously in amplitude, shape, duration, and direction.

We conclude that atrial signals reaching the AV node during fibrillation have complex patterns that differ in different patients or in the same patient under different circumstances. Drugs like digitalis,[45] quinidine, amiodarone, and others also affect the electrical behavior of the fibrillating atria, and thus the pattern of the signals that reach and surround the AV node.

AV NODAL FUNCTION IN ATRIAL FIBRILLATION

Since Engelmann[46] at the end of previous century introduced the word *Leitung* for the functional or anatomical connection between atria and ventricles, the coupling between ventricular and atrial excitation and contraction has been described in terms of conduction. *Leitung* may be translated as "connection" (cable or wire) or indeed "conduction"—the transport of electrons as later expressed by Hoffman and Cranefield in their cable theory for AV nodal function.[47]

Concealed Conduction

Engelmann was the first to observe and describe what is called today concealed conduction. While studying the effect of atrial extrasystoles on the contractions of the ventricles of isolated frog hearts, he noticed that every effective atrial contraction, even if it did not elicit a ventricular systole, prolonged the subsequent AV interval.

Langendorf[4] in 1948 observed the same phenomenon in clinical electrocardiograms and named the phenomenon "concealed conduction." According to Fisch,[48] concealed conduc-

tion is incomplete conduction coupled with an unexpected behavior of the subsequent impulse.

Hoffman and Cranefield[49] introduced the concept of decremental conduction to explain AV nodal delay during sinus rhythm. Concealed conduction and decremental conduction were recognized as the basic mechanisms by which the AV node slows the ventricular rate during atrial fibrillation.[50]

Moore[51] and Mazgalev et al.[52] showed concealed conduction using microelectrodes in isolated rabbit preparations. Short RR intervals were associated with lesser or absent concealment, whereas several atrial impulses were concealed during long cycles. There can be no doubt about the essential role of the AV node to slow down the rate of the fibrillating atria. This is best demonstrated in patients with the Wolff-Parkinson-White syndrome, atrial fibrillation, and conduction through the accessory pathway[28,53] in whom ventricular rates may reach values of 300/min and can produce ventricular fibrillation and sudden death.[54,55]

The AV Node as a Biological Oscillator

For many years there was little reason to doubt the Langendorf–Moore concept of concealed conduction as the slowing mechanism of the AV node. However, Grant[56] and James and his group[57,58] brought forward alternative mechanisms that could explain AV nodal function without viewing the AV conduction system as an electrical cable with a high-resistance site in the AV node. Grant[56] suggested that the AV node, like the sinus node, may behave like a relaxation oscillator and thus be modulated by outside influences.[59,60] In 1983, Cohen et al.[61] published a model that characterized the behavior of the AV node as an equivalent cell in terms of a hypothetical transmembrane potential—in other words, as an electrotonically modulated pacemaker. This model was attractive because it could easily explain the characteristics of the ventricular rhythm in patients with atrial fibrillation, without necessarily adopting the concealed conduction theory. In 1986, Van der Tweel et al.[62] presented experimental evidence that the function of the canine AV node could be described as a periodically perturbed, biological oscillator.

The Compensatory Pause

Langendorf,[63] Pritchett et al.[64] and others[65,66] demonstrated that after ventricular extrasystoles the ventricular cycle was lengthened also in the presence of atrial fibrillation.[63] Langendorf called this phenomenon the compensatory pause in atrial fibrillation. It was believed to be caused by lengthening of the AV node refractory period due to retrograde concealed conduction into the AV node of the spontaneous or artificially evoked ventricular extrasystole. However, Moore and Spear[67] and Akhtar and coworkers[68,69] showed that properly timed retrograde concealed conduction facilitates rather than slows AV nodal anterograde conduction.

Renewed doubt in the validity of concealed conduction theory as an explanation for the ventricular rate and rhythm in atrial fibrillation originated from the work of Wittkampf et al.[70] They found that ventricular pacing at intervals almost twice as long as the shortest spontaneous RR intervals in patients with atrial fibrillation and normal AV conduction could block all anterograde conduction, resulting in a pacemaker rhythm without any anterogradely conducted QRS complexes (Fig. 15.2). These observations cannot be explained by the classical AV nodal "filter" theory, despite the defense of concealed conduction by Dreifus and Mazgalev[71] in an editorial that accompanied Wittkampf's paper.[70]

In further studies, Wittkampf and coworkers,[72,73] using induced ventricular extrasystoles, obtained further evidence that in patients with atrial fibrillation, concealed anterograde conduction at different levels in the AV node is unlikely. The apparent ability to reset a random discharge cycle in the AV node by ventricular extrasystoles suggests that the distal side of a weakly coupled area inside the AV node behaves as a pacemaker for the ventricular rhythm during atrial fibrillation.
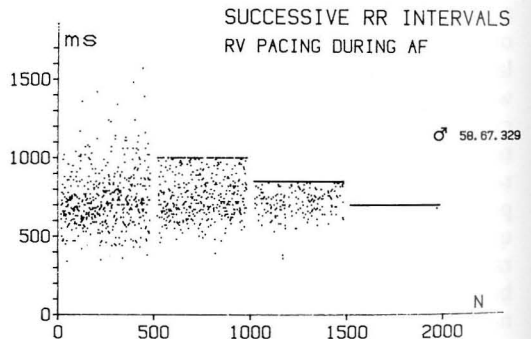

FIGURE 15.2 Successive RR intervals in a patient with atrial fibrillation before (first 500 cycles) and during pacing of the right ventricle with a pacing interval of 1,000 ms, 850 ms, and 700 ms (cycles 500–2,000). At a pacing interval of 700 ms (last 500 cycles) all anterograde "conduction" ceased and the rhythm became regular. *Reprinted from Wittkampf et al.,*[70] *with permission.*

Scaling in the AV Junction?

Scaling of atrial impulses in the AV junction has been widely accepted as the cause of the random and relatively slow ventricular response in patients with atrial fibrillation.[29,30] Wittkampf et al.[74,75] studied ventricular rhythm in patients with atrial fibrillation under various circumstances known to modulate AV nodal conduction characteristics. With a fixed scaling factor (ratio between atrial and ventricular rates), the relative variability of the atrial and ventricular cycle length should relate to the square root of the scaling factor.[76] This principle is the basic mechanism of the atomic clock. However, a linear relationship between variability and ventricular cycle length was found with an almost constant relative variability of 22%. In any scaling process in which the cumulative effect of randomly irregular impulses of randomly varying magnitude would lead to ventricular activation, individual variations would partly compensate each other and thus tend to stabilize the rhythm at longer average cycle lengths when on the average more impulses are required to generate the next ventricular depolarization. Thus, a proportional increase in absolute variability is not to be expected if longer intervals are derived from randomly irregular short intervals by such a process of scaling.

When a more frequent invasion of the AV node by atrial impulses (for instance during digitalis treatment) would be responsible for a slower ventricular rate, the average scaling factor would be more than proportionally higher in patients with a long average ventricular cycle length than in those with a relatively fast ventricular rate under similar circumstances. This would have to result in even greater reduction of relative variability at slow ventricular rates. Figure 15.3 shows that this is not the case. Due to the effect of digitalis treatment, average cycle length has increased. At the same time the width of the histogram (standard deviation) also has increased. In atrial fibrillation, the irregularity of the ventricular rhythm increases linearly with the ventricular rate. In other words, all patients with atrial fibrillation have about the same irregularity of their ventricular rhythm irrespective of their ventricular rate. An unusual and odd filtering process has to be assumed to explain such a linear relationship between average cycle length and standard deviation. This suggests to us that scaling as traditionally conceived almost certainly does not take place in the AV junction. We realize that these findings disagree with our former ideas,[30] the views of Dreifus and Mazgalev,[71] and the conclusions derived from the experimental findings of Moore,[51] Janse,[77] and others[78,79] in in vitro preparations.

Alternative Explanation

The linear relationship between average cycle length and absolute variability at different randomly irregular atrial and ventricular rhythms suggests that randomly irregular fibrillatory atrial impulses are not conducted through the AV junction but rather impart to cells within the AV junction a similarly irregular behavior, but on a slower time scale. When all intervals between atrial impulses are multiplied by a constant factor, then both average cycle length and standard deviation are multiplied by the same factor, and consequently the relative variability remains constant. The relationship observed by us seems to be the expression of an intrinsic property of AV nodal cells which is responsible for both the average ventricular cycle length and the standard deviation during atrial fibrillation. Although these findings and this hypothesis are in agreement with the AV nodal pacemaker theory, they do not support the mechanism of phase 4 electrotonic modulation that would also result in a decrease of relative irregularity with increasing ventricular cycle length.[6,61,80] Our findings could be explained by electrotonic inhibition and summation in AV nodal cells,[81,82] a mechanism requiring further experimental support. We restipulate the characteristics of AV nodal function during atrial fibrillation as follows: (a) complete blocking of all anterograde conduction during right ventricular pacing at pacing intervals that are twice as long as the spontaneous short RR intervals; (b) the reset of the AV nodal activation sequence following ventricular extrasystoles; and (c) the absence of scaling of the atrial impulses as the cause of the slower ventricular rate.

This suggests to us that the classical concept of propagation through the AV junction by concealed and decremental conduction in the AV node resulting in scaling down of the atrial rate does not explain the ventricular rate and rhythm in patients with atrial fibrillation. A region within the AV node seems to determine ventricular rate and rhythm modulated by the inefficient electrical impulses of the fibrillating atria.[60]

It should be mentioned that also during sinus rhythm the AV node may not conduct the well-organized atrial impulse in a generally accepted manner. This is apparent from the mismatch between the heart size and the PR interval.[83,84]

As early as 1913, Waller[85] drew attention to the correlation between the size of the animal and the "aurioculoventricular" interval. Clark in 1927[86] was struck by the fact that the PR interval varies so little in different animals. There is, paradoxically, a comparatively short PR interval in hearts of large animals. Since the heart weight is closely and linearly related to the body weight,[87,88] the latter can be substituted by the
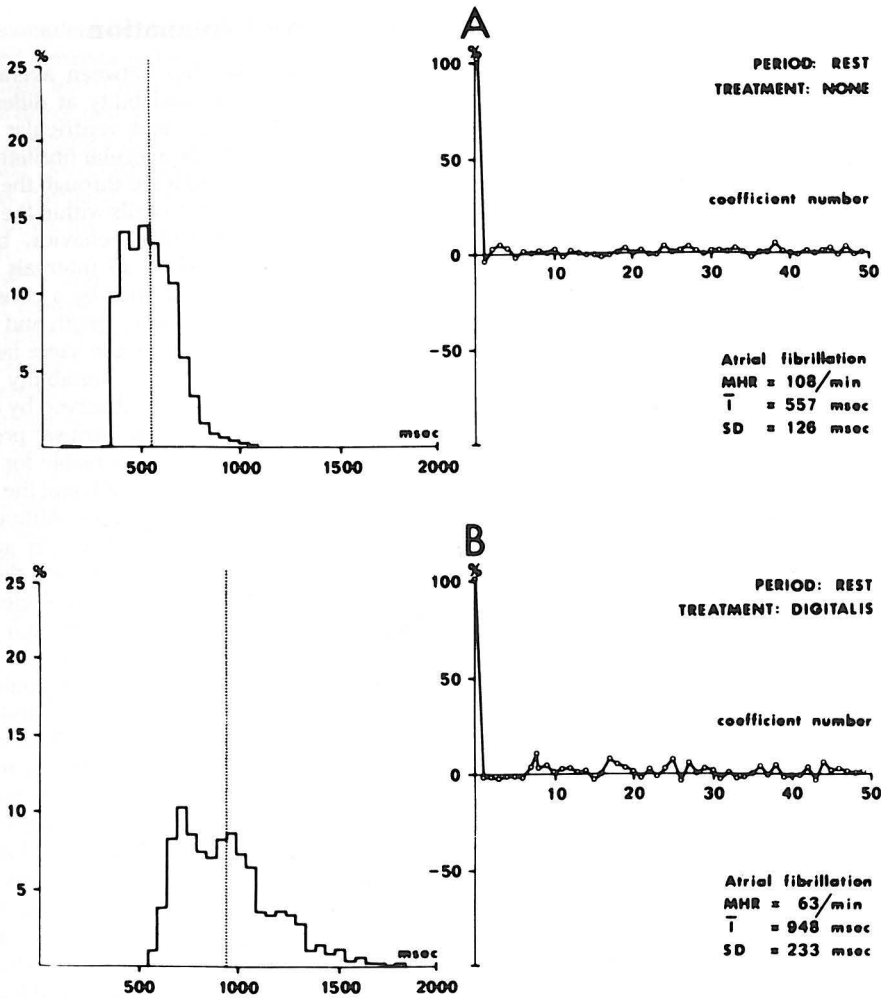
A

PERIOD: REST
TREATMENT: NONE

coefficient number

Atrial fibrillation
MHR = 108/min
Ī = 557 msec
SD = 126 msec

B

PERIOD: REST
TREATMENT: DIGITALIS

coefficient number

Atrial fibrillation
MHR = 63/min
Ī = 948 msec
SD = 233 msec

FIGURE 15.3 Histogram and autocorrelogram of the RR intervals of a patient with atrial fibrillation at rest without (**A**) and with (**B**) digitalis treatment. The autocorrelogram is unchanged; the ventricular rhythm remains random, despite change in form and shift to the right of the histogram. *Reprinted from Bootsma et al.,*[30] *with permission.*

former and the mismatch between the PR interval and the heart weight becomes evident.[83]

The length of the AV conduction system can be approximated by the third root of heart weight.[80] The relationship between PR interval and the third root of heart weight is shown in Figure 15.4. The S-shape of this relationship indicates a relatively long AV delay in small mammals and a relatively short AV delay in large mammals. Assuming a more or less constant conduction velocity in the His-Purkinje system,[89] although differences of some orders of magnitude may be also present,[90,91] the contribution of the AV node to the total AV delay (PR interval) in small mammals is relatively large, and relatively

small in large mammals such as horses, elephants, and whales. From Kawamura's work[92] it became apparent that small mammals have relatively large AV nodes, whereas large mammals have relatively small ones. James[60] made it plausible that the AV nodes in large mammals contain more fibrous tissue (thus fewer P cells) than the AV nodes in small mammals. These two findings may offer at least in part a morphological substrate for the mismatch between the PR interval and the body (heart) size. If the conduction through the AV system were to take place as conceived by Hoffman and Cranefield,[47] the relationship between PR interval and heart size would be almost certainly different.

PR interval [ms]

FIGURE 15.4 Relationship between PR interval and the third root of heart weight. Values obtained from Altman and Dittmer.[118]
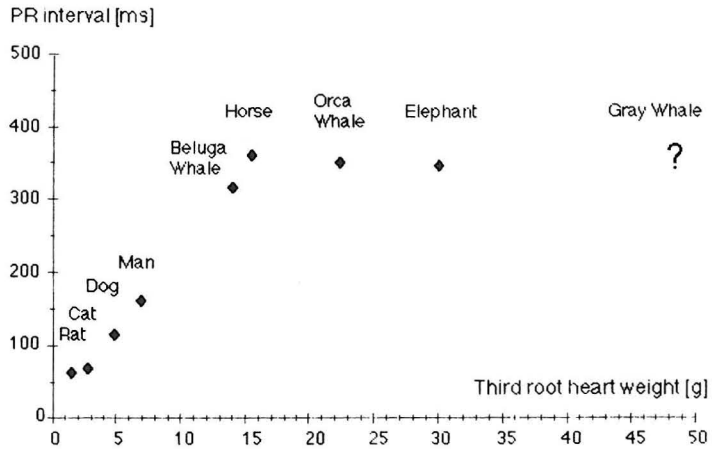
THE VENTRICULAR RHYTHM IN ATRIAL FIBRILLATION

The most striking clinical feature of atrial fibrillation is the irregularity of the pulse. Although the complete irregularity of the heart was discovered and established long ago, the advent of computers enabled the ventricular rhythm to be analyzed more accurately and its mathematical properties to be established. The introduction of sophisticated time sequence analyzing techniques in the early 1950s stimulated several groups of investigators to study the irregular ventricular rhythm in atrial fibrillation.[30,93–96] The results of these studies were sometimes conflicting and created confusion and even controversies.[97,98] The differences in the results were probably due to, or at least influenced by, the choice of the statistical techniques, the selection of patients, and the use of induced (artificial) atrial fibrillation in atria that would otherwise not have fibrillated. Moreover, high-frequency atrial stimulation was employed in healthy dogs to simulate atrial fibrillation and to obtain irregular ventricular rhythms that looked like the rhythms obtained at the bedside, but may not have represented real-life situations.

Human Patients

In a study published in 1970,[30] we used serial autocorrelograms and histograms to analyze the ventricular rhythm of patients with sustained atrial fibrillation before and during digitalis treatment at rest and during exercise. The results of this study led to the conclusion that the ventricular rhythm in patients with uncomplicated atrial fibrillation is random where randomness is defined as a time series having mutually indepen-

dent intervals. In Figure 15.3, reproduced from this paper, the histogram and autocorrelogram of the RR intervals of a patient with atrial fibrillation is shown before (A) and during (B) digitalis treatment. Despite a shift to the right and significant changes in the shape of the histogram due to digitalis treatment, the autocorrelogram was not affected. All correlation coefficients remained at zero before and during digitalis treatment, and thus the ventricular rhythm remained random. The same was true for the situations before and during exercise, namely, there was a change in the histogram, but the ventricular rhythm remained random. Different interventions and different drugs like digitalis, quinidine, verapamil, and β-blockers change the histogram but do not affect the random pattern of the ventricular rhythm in human patients.

Horses and Dogs

In a subsequent study[43] we demonstrated that dogs with true atrial fibrillation on the basis of mitral incompetence also had a random ventricular rhythm. Atrial fibrillation induced by rapid atrial stimulation, however, although resulting in an irregular ventricular rhythm, did not create randomness of the successive RR intervals. Horses are known to develop atrial fibrillation, usually on the basis of some form of myocardial disease.[15] It is of considerable interest that horses with atrial fibrillation at rest, with or without digitalis treatment, have signs of periodicity in their autocorrelogram (Fig. 15.5).[99] This periodicity can be abolished by atropine and quinidine, drugs that cause an increase in ventricular rate. From these observations we concluded that a considerable drop in blood pressure caused by
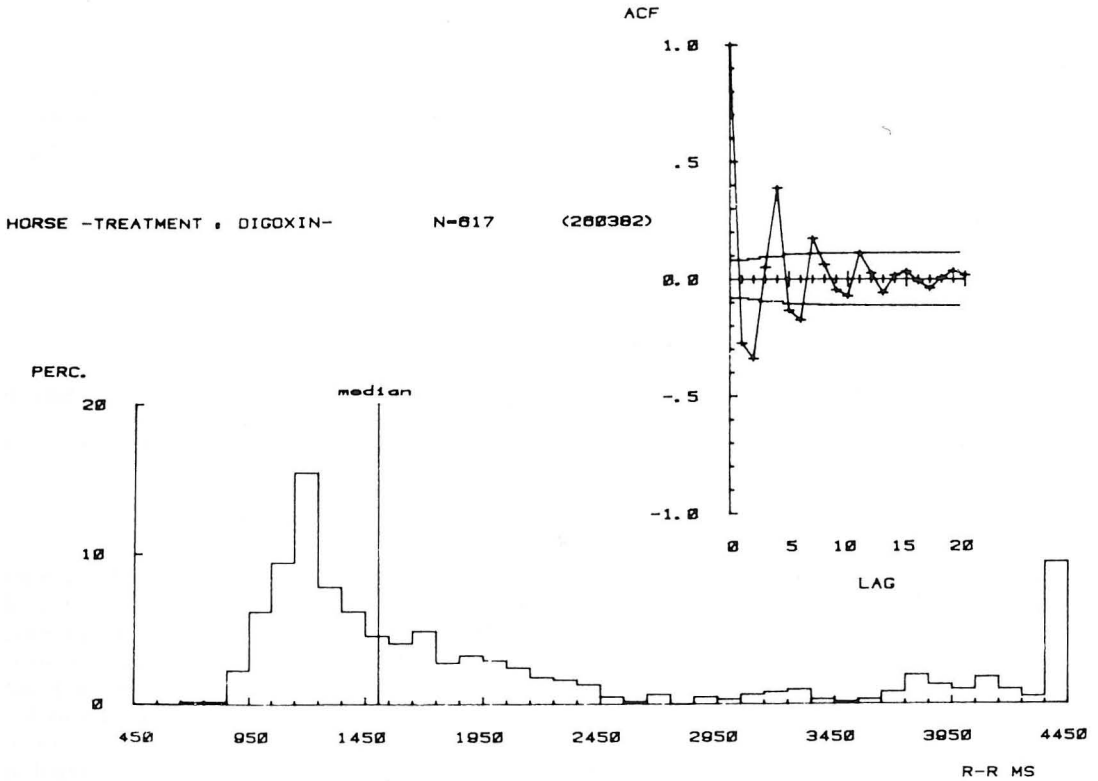
FIGURE 15.5 Histogram (left) and serial autocorrelogram (right upper corner) of a horse with atrial fibrillation during digitalis treatment. Note the large number of much longer intervals (4,450 ms or more) and the strong periodicity in the autocorrelogram. *Reprinted from Meijler et al.,*[99] with permission.

very long RR intervals (up to 5 s) in horses with atrial fibrillation creates autonomic nervous interference with AV nodal propagation properties through baroreceptor triggering.[99] Our overall conclusion was that the cause of ventricular irregularity resides somewhere else than in the AV conduction system, and we offered the hypothesis that randomly spaced atrial impulses of random strength reaching the AV node from random directions are responsible for the renewal process of the RR interval sequence.[30] This opinion was strengthened by the fact that the fast ventricular rhythm is also random in patients with Wolff-Parkinson-White syndrome and atrial fibrillation and conduction through the bypass,[28] while patients and dogs with ventricular fibrillation during heart–lung bypass turned out to have a random atrial rhythm; again randomness is defined as a time series without mutually dependent intervals.[100]

We have concluded that the essential role of the AV node in atrial fibrillation is restricted to the process of changing the rapid atrial rhythm into a slower ventricular rhythm, probably by some form of electrotonic modulation of an AV nodal pacemaker.

DELIRIUM CORDIS

Apart from the lack of insight into the AV nodal function, another baffling puzzle is the regulation of cardiac output during atrial fibrillation, especially in the presence of valvular disease. It is well known that atrial fibrillation may be totally unnoticed by the patient who may be unaware of an irregular heart beat, and may not be limited in daily physical activities. Often there are no signs of heart failure; cardiac output may be adequate and blood pressure remain normal, even during severe exertion.[50] Nevertheless, atrial fibrillation was discovered not only because the pulse was irregular but also because the arterial pulsations differed in form and size. This led Hering[20] and also Wenckebach[101] to the introduction of the term "delirium cordis." It is fascinating to learn how at the beginning of this century, that is, before the introduction of the electrocardiograph, the irregularity and inequality of the

pulse occupied the minds of the pioneers in cardiology.[1,20,22,101,102]

The Frank–Starling Mechanism

In 1915, Einthoven and Korteweg[102] demonstrated that the amplitude of the pulse wave was related to the length of the preceding heart period. In the following decades, the relationship between duration of the cardiac cycle and variations in hemodynamics in patients with atrial fibrillation was explained by the effect of varying degrees of diastolic filling on the contractile force of the heart (Frank–Starling mechanism).[103,104] In 1960, Braunwald and associates[105] reasoned that it was "unlikely that the duration of the preceding diastole, per se, determines the characteristics of the subsequent ventricular contraction" but that "Starling's law of the heart operates in patients with mitral stenosis and atrial fibrillation on a beat to beat basis."

In 1968 we showed[106] that in isolated Langendorff-perfused rat hearts in which Starling's law cannot operate, an induced random rhythm creates the same variability of ventricular contractions as observed in patients with atrial fibrillation (Fig. 15.6). In agreement with Braunwald et al.,[105] we found in patients with atrial fibrillation and mitral stenosis that left ventricular end diastolic pressure and dimensions may be closely related to the duration of the diastolic pause. However, in patients with atrial fibrillation but without mitral stenosis, the left ventricle attains maximum volume early in diastole and remains constant and independent of the duration of the diastole. Left ventricular beat-to-beat variations are thus unaffected by preload.[107–109]
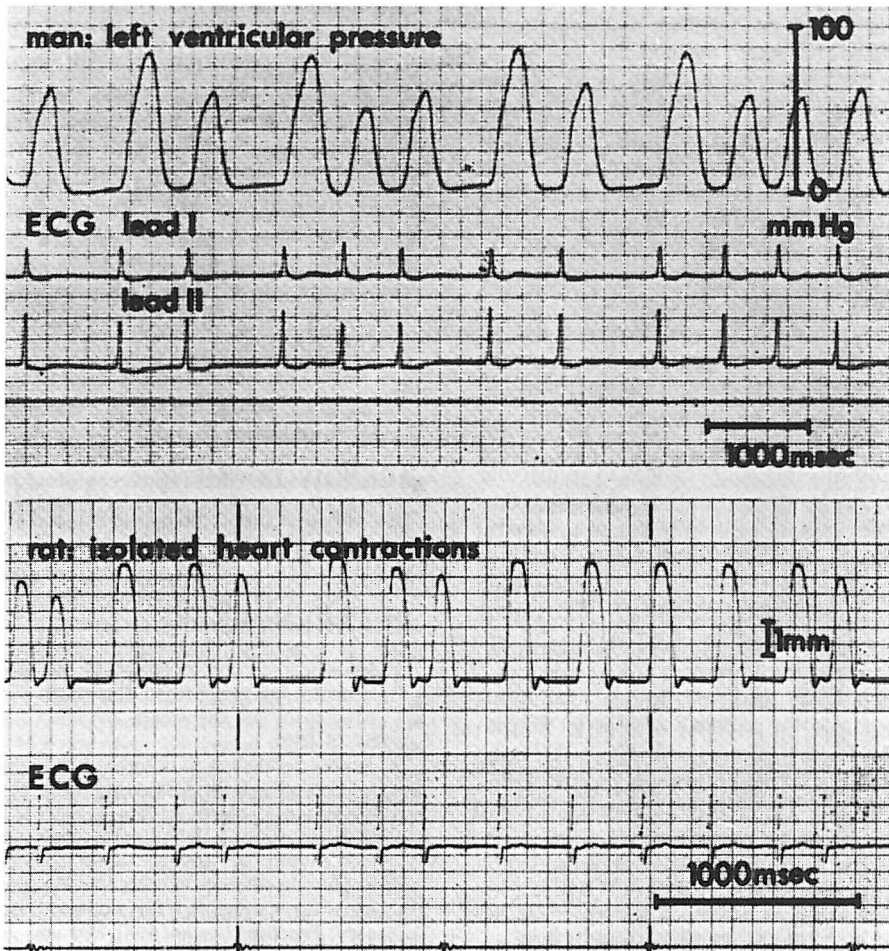

FIGURE 15.6 Left ventricular pressure of a patient with atrial fibrillation (upper curve) and contractions of an isolated rat heart (lower curve) stimulated with a (ventricular) rhythm from a patient with atrial fibrillation. (For further details, see text). *Reprinted from Meijler et al.,*[106] *with permission.*

Postextrasystolic Potentiation

During atrial fibrillation, left ventricular contractions are mainly dependent on cycle length. Brooks in 1960[110] introduced the term "post-extrasystolic potentiation," a physiological phenomenon that describes the strengthening effect of a short RR interval on the subsequent ventricular contraction. The opposite is also true: a longer-than-average interval depotentiates or weakens the subsequent contraction.[111] The weakening after long intervals is less pronounced than the potentiation after short intervals.

The RR interval histogram in atrial fibrillation (Fig. 15.3) shows that there are more shorter-than-average intervals than longer-than-average ones. The result of this is that beat-to-beat variations in atrial fibrillation are positively related to the preceding RR interval and inversely related to the pre-preceding interval(s).[106,112] The effect of RR interval duration on contractile behavior of the heart is quite complicated but can be accounted for by the potentiation and depotentiation effects.[113,114]

When we consider hemodynamic parameters like stroke volume or arterial blood pressure in relation to preceding RR intervals, it should be realized that long RR intervals diminish aortic impedance, while ventricular contractions after a short RR interval may face a high aortic impedance.[115] This, of course, tends to strengthen the first coefficient of any RR interval/hemodynamic parameter correlation.

Despite the evolving knowledge of the relation between stroke volume and the preceding RR intervals,[108,113,116] we still do not fully understand the regulation of the circulation in patients with atrial fibrillation at rest and during exercise and the effects of changes in ventricular rates induced by drugs such as digitalis, verapamil, β-blockers, or quinidine. Since in general cardiac output tends to be adequate within a wide range of ventricular rates,[50] one is tempted to assume a loose association between cardiac output and ventricular rate and rhythm in patients with atrial fibrillation.

We conclude that beat-to-beat variations (delirium cordis) in patients with atrial fibrillation can be explained satisfactorily on the basis of potentiation and depotentiation of myocardial contractility and cycle-length-dependent aortic impedance. However, the maintenance of an adequate cardiac output and blood pressure is still inadequately explained.

FINAL REMARKS

Although atrial fibrillation is the most frequently occurring arrhythmia, we still do not know how the AV node transforms fast irregular atrial rhythm into a random ventricular rhythm at a rate compatible with life. We also do not know how in patients with atrial fibrillation cardiac output is regulated and adequate circulation is maintained. After almost 100 years of research into the riddles of atrial fibrillation, the picture of our metaphoric elephant is still opaque, and the dimness of our vision still obscures the intervening obstacles.[22]

CONCLUSION

Atrial fibrillation is a commonly observed cardiac arrhythmia that shows the following characteristics:

(a) Fibrillation of the atria is caused by electrical inhomogeneity of the atrial myocardial cells.

(b) Transformation of a rapid atrial rate into a slower ventricular rate that is compatible with maintenance of life. Recent findings make it unlikely that concealed and/or decremental conduction in the AV junction takes place during atrial fibrillation.

(c) Random ventricular rhythm is created by an erratic electrical behavior of the atria. The atrial impulses impart to the AV node, possibly by electrotonic modulation, a random activation sequence that is much slower than the rate of the atrial impulses.

(d) While ventricular rhythm is random in atrial fibrillation, the ventricular contractions correlate up to the second (and sometimes third) coefficient with preceding RR intervals. This correlation is based on postextrasystolic potentiation and depotentiation following long intervals.

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