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Lessons from Comparative Studies of Atrial Fibrillation in Dog, Human, and Horse

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Since its first description in 1903 by Hering,[1] the irregularity of the heart beat has been the most striking characteristic of atrial fibrillation and has been subject of many studies.[2-6] To quote Selzer, "Atrial fibrillation is the grandfather of cardiac arrhythmias."[7] It is an arrhythmia that 1) often complicates rheumatic heart disease, 2) is a frequent complication of coronary heart disease and diabetes, and 3) may accompany hyperthyroidism.[8-10]

Moe[11-13] has considerably contributed to our understanding of atrial fibrillation. He, like Burn,[14] made it plausible that fibrillation arises because the electrical activity generated by the fibers excites one another. The multiple wavelet hypothesis still seems the best explanation for what we observe electrophysiologically during (atrial) fibrillation (see Chapter 30). Our own observations[15] using signal analysis techniques in experimental ventricular fibrillation support the ideas formulated by Moe nearly 25 years earlier. Nevertheless, the true pathophysiologic mechanisms are basically unknown. Similarly the role of the AV node-His conduction system in atrial fibrillation is not fully understood.[16] The purpose of this paper is to present observations obtained during comparative studies in dogs, humans, and horses with atrial fibrillation that may prove helpful in explaining the irregular pattern of the ventricular rhythm and may also contribute to a more rational therapy of atrial fibrillation.

METHODS

In all of our studies of dogs, humans, and horses with atrial fibrillation, we used the histogram and serial autocorrelogram (SAC) of R-R intervals for ventricular rhythm analysis. The ECG was recorded on magnetic tape using the extremity leads with the tallest R waves for QRS detection and computation of R-R intervals. ECG recordings from dogs were obtained either during superficial anesthesia or, whenever possible, while the animals were conscious and lying quietly on their sides. If not otherwise specified, the human ECG was always recorded in the supine position under steady-state conditions in a temperature-controlled room. The ECG recordings of horses were obtained while the horses were standing quietly. As a rule the records were long enough to obtain approximately 1000 R-R intervals that were needed for acceptable data analysis. Histograms and SACs were produced by digital computer with a method described previously.[17-19]

RESULTS

Atrial Fibrillation in Dogs

Spontaneous atrial fibrillation in dogs is a common occurrence in veterinary medicine.[20] The ventricular rhythm has the same characteristics as that found in man.[18] Figure 1 is a typical example of the results obtained. It can be seen that the histogram is positively skewed as in man and that the SAC shows the well-known pattern of randomness,[17,18] which is indicated by the fact that with the exception of coefficient 0 all further coefficients do not differ statistically from zero. The histogram shows that the shortest R-R intervals are in the order of 250 msec and that the longest have durations of about 750 msec. The median R-R interval is about 450 msec. The coefficient of variation (standard deviation as a proportion of the mean) = 0.19. These data are representative for the study of six dogs prior to the institution of therapy.

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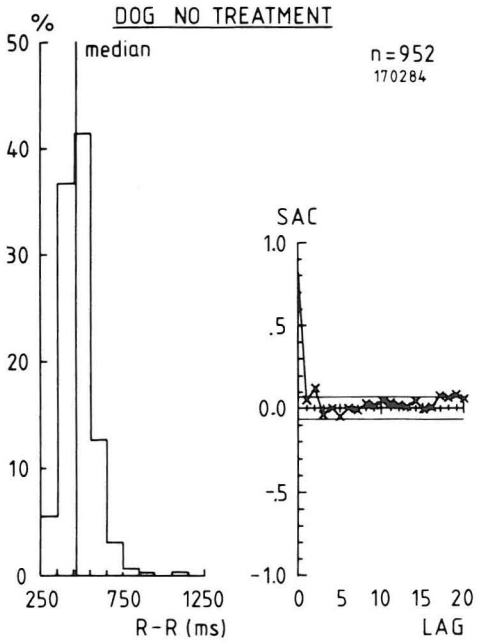

Figure 1. Representative histogram (*left*) and serial autocorrelogram (*right*) of an untreated dog with atrial fibrillation. Lag stands for coefficient number, SAC for serial autocorrelogram. The lines parallel to the x-axis in the SAC represent the 95 percent confidence limits. Within those limits the correlation coefficients are statistically not different from zero. The coefficient of variation is 0.19.

Atrial Fibrillation in Humans

Our studies published in 1968 indicated that the ventricular rhythm in humans was not only irregular, but that the irregularity had a random pattern.[21] Subsequent studies included approximately 200 patients, before and after a variety of drugs, before and after exercise, in supine and erect positions, and also included patients with atrial fibrillation complicating Wolff-Parkinson-White syndrome (WPW). Among the drugs studied were digitalis, quinidine, propranolol, verapamil, atropine, and amiodarone. Under all these circumstances the ventricular rhythm remained random, but with widely varying histograms. Nonrandom patterns of the ventricular rhythm during atrial fibrillation may be the result of AV block and escape of an AV junctional pacemaker with or without ventricular ectopy.[22] Similarly in patients not in a steady state (e.g., at the beginning of or immediately after exercise),[17,23] a nonrandom rhythm may emerge. In nontreated patients (Figure 2), the histogram is always positively skewed. The median R-R interval is on the order of 650 msec with R-R intervals varying from 350 to 1000 msec. The coefficient of variation is 0.17, thus approximately equal to that in the dog.

Atrial Fibrillation in Horses

From Moe's concepts,[11–13] it follows that the larger the heart the more easily it will fibrillate. For this reason we included horses in our studies of atrial fibrillation.[24,25] We analyzed ventricular rhythm in eight horses with spontaneous atrial fibrillation.[19] The histograms were similarly positively skewed with median R-R intervals of approximately 1000 msec, with a range from 400–600 msec to 5 sec.

This wide range causes a coefficient of variation of 0.47;

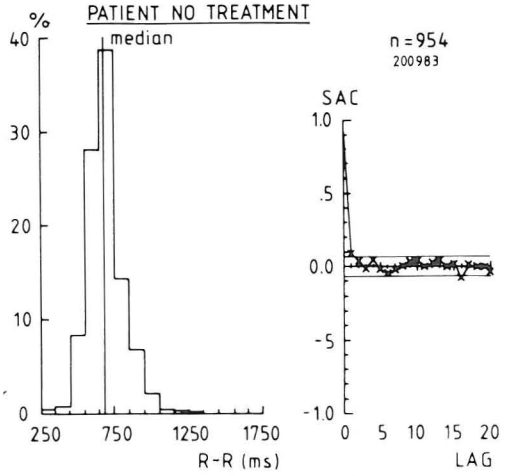

Figure 2. Representative histogram (*left*) and SAC (*right*) of a human patient with atrial fibrillation, but without receiving any medication. The class width and the scale of the x-axis of the histogram is identical to that in Figure 1. The median R-R interval is considerably longer than in the dog. The SAC shows that the ventricular rhythm is random. The coefficient of variation is 0.17.

considerably larger than in dogs and humans. A typical example is given in Figure 3. In contrast to dogs and humans, the SAC demonstrates that the ventricular rhythm in horses with atrial fibrillation in the absence of extrasystoles and/or AV junctional rhythms is not completely random. Long R-R intervals alternate with four to five short ones, causing a nonrandom pattern of the ventricular rhythm. These episodes of periodicity can be enforced by digitalis and abolished by quinidine and atropine. Digitalis increases the incidence and duration of long R-R intervals. R-R intervals of close to 5 seconds are fairly common. At the same time, digitalis increases the duration of the short R-R intervals. Quinidine and atropine shorten the R-R intervals and eliminate those exceeding 2 seconds.

In one horse we were able to measure the intra-arterial pressure and found large fluctuations as the R-R intervals varied from less than 500 msec to over 3 sec. During the long R-R intervals, the blood pressure dropped to values of 50 mm Hg or lower.[19] By correlating respiration rate with the ventricular rhythm in one of the horses with atrial fibrillation, an effect of respiration on the ventricular rhythm could be excluded as the cause of periodicity in the SAC.

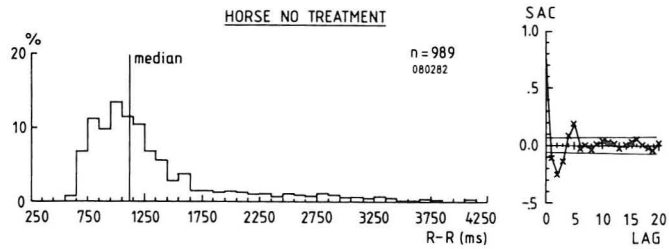

Figure 3. Representative histogram (*left*) and SAC (*right*) of a horse with atrial fibrillation. The horse received no medication. Again the histogram has the same interval scale as in Figures 1 and 2. The median R-R interval is over 1100 msec. The long/short R-R interval ratio is about 5. The SAC shows periodicity. For further details see the text. The coefficient of variation is 0.47.

DISCUSSION

THE MECHANISM OF RANDOMNESS

In canine and human patients with atrial fibrillation, digitalis, nor quinidine nor exercise affects the random character of the ventricular response.[16–18] Also a change in the patient's position (supine or erect) does not change the random ventricular pattern (Figure 4) during atrial fibrillation.

The random characteristics of the ventricular rhythm are consistent with the following findings:

1. Signal analysis of the right atrial bipolar electrogram obtained during atrial fibrillation in man demonstrates that the atrial excitation process has noiselike qualities.[26] This, however, does not exclude the possibility that parts of the left and/or right atrial muscle may have other electrical properties,[27] although in the majority of cases studied by us to date, we always found the same pattern, at least in the right atrium.
2. Adaptation of the AV conduction time to stepwise atrial rate changes induced by programmed stimulation depends on time rather than on the number of cardiac cycles.[28,29] In other words, the time constant of AV conduction adaptation is more or less independent of changes in atrial stimulation rate or of intervals between atrial impulses.
3. Changes in AV conduction time induced by changes in atrial rate and/or rhythm show a short time constant ("memory"),[29,30] memory being the time the AV conduction system needs to adapt to changes in P-P (AA) intervals. In humans, AV nodal memory is usually less than 2 seconds. Thus the effect of changes in intervals between conducted atrial impulses on subsequent AV conduction lasts too short a time to affect the interval between the following conducted impulses. As a consequence, during atrial fibrillation, AV conduction adaptation cannot impose a long-term influence on the sequence of conducted atrial impulses. However, when a high ventricular rate is present one may sometimes observe a slightly positive first correlation coefficient.[17,23,31]
4. In patients with WPW syndrome and atrial fibrillation and conduction via the bypass tract, the ventricular rhythm is often random as well. However, the histogram loses its skewed appearance and the ratio between short and long R-R intervals is seldom over 1.5–2.
5. Carotid sinus nerve stimulation evoked an increase of the AV conduction time after a latency of 0.8–1.6 seconds.[32] Therefore, the baroreceptor response in man to blood pressure variations such as seen in patients with atrial fibrillation, occurs too late or may be too insensitive to allow for interference with AV conduction. R-R intervals in patients with atrial fibrillation are seldom longer than 1.6 seconds and only with high doses of digitalis may reach values of 2.0 seconds. Moreover, even during R-R intervals of 2 seconds, blood pressure usually does not reach values low enough to affect the autonomic nervous system.[33] Therefore, changes in AV conduction properties by beat-to-beat blood pressure variations during atrial fibrillation are not observed.
6. The presence of periodicity in the ventricular rhythm of horses with atrial fibrillation supports the explanation given for the random pattern of the ventricular rhythm in the dog and man with atrial fibrillation. R-R intervals of 3 seconds or more during atrial fibrillation in horses are almost certainly long enough to enable the autonomic nervous system to modulate AV nodal conduction properties. At the same time, during those long R-R intervals blood pressure may fall to values that induce vagal inhibition and thereby increase AV nodal conductivity and/or reduce the number of atrial impulses that reach the AV junction. It is of interest to note that digitalis, by increasing R-R interval duration, enforces the periodicity in the SAC, while atropine and quinidine have exactly the opposite effect.[19] Atropine changes the ventricular rhythm of a horse with atrial fibrillation into one that resembles those of humans and dogs.

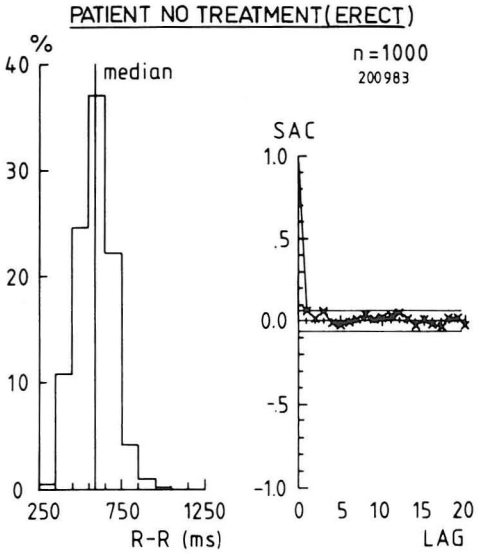

Figure 4. Histogram and SAC of the patient shown in Figure 2, but now while standing erectly. It can be seen that the median R-R interval has shortened, but the SAC does show that the ventricular rhythm has remained random.

In summary the ventricular rhythm during atrial fibrillation in dog and man is random because the atrial excitation process itself is probably random, AV nodal memory is in general too short to interfere with the random pattern of the conducted impulses, and the response of the human autonomic nervous system to beat-to-beat blood pressure changes is too slow and too insensitive to affect AV conduction properties.

THE HISTOGRAM

The changes in histogram due to various drugs or varying conditions such as exercise, while the random pattern of the ventricular response was maintained, need further comments.

1. Slowing of the ventricular rate during atrial fibrillation by digitalis can be explained by its vagal effect on the atrial myocardium and, to a lesser extent, by the increased refractory period of the AV junction.[34] Long R-R intervals during digitalis treatment are probably caused by the increased number of atrial fibrillatory waves that reach the AV junction in a given unit of time. This causes more repetitive concealed conduction in the AV junction, resulting in longer R-R intervals. Even if digitalis did not influence the electrophysiologic properties of the AV con-

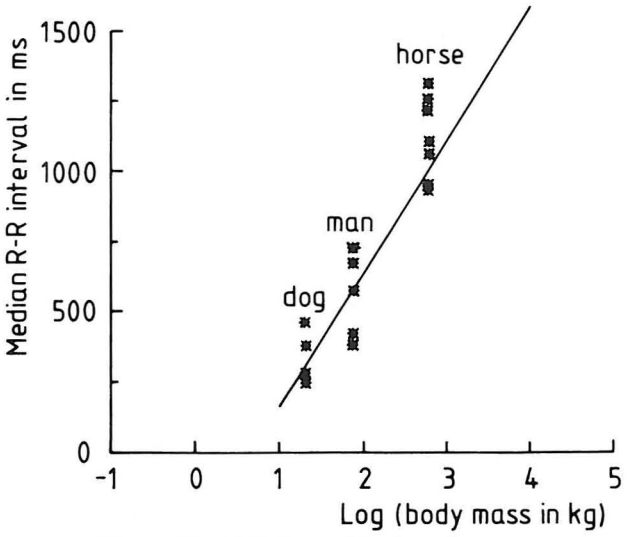

Figure 5. The median R-R interval in dogs, humans, and horses with atrial fibrillation. It should be noted that the x-axis has a log scale and the y-axis a linear scale, showing the disproportion between functions of the AV conduction systems and the sizes of the species studied.

duction system, the increase in the number of atrial impulses that reach the AV junction suffices to explain the increased duration of R-R intervals by the mechanism of concealment.

2. Quinidine with its atropine-like action[35] and atropine itself not only shorten the AV node refractory period, but also cause a decrease in the number of atrial impulses that reach the AV junction in a given unit of time. This probably results in less concealed conduction and thus in shorter R-R intervals.
3. Also the effects of other antiarrhythmic drugs such as verapamil or amiodarone on the ventricular rhythm during atrial fibrillation can be explained by their action on the atrial myocardium and, to a lesser extent, on the electrophysiologic properties of the AV conduction system.[36]
4. Conditions such as body position and exercise affect the ventricular histogram during atrial fibrillation, probably because they alter the long-term autonomic nervous influences on the atrial myocardium and/or the AV junction. Decreased vagal tone shortens the refractory period of the AV node and lengthens the refractory period of atrial myocardium.[37] The latter probably diminishes the number of atrial impulses that reach the AV junction, thereby diminishing concealed conduction into the AV node, which in turn results in a higher average ventricular rate.

The Median R-R Interval

Comparative studies of RR interval analyses during atrial fibrillation demonstrate that as heart size increases the median R-R interval increases from about 400 to 600 to 1000 msec (Figure 5). The coefficient of variation is almost equal in canines and humans with atrial fibrillation in the absence of medication. The horse has a larger coefficient of variation due to the long R-R intervals. When the long R-R intervals disappear, for instance after atropine administration, the coefficient of variation diminishes and the histogram (like the SAC) of the horse begins to resemble that of canines and humans.

The coefficient of variation is related to what Billette et al. call R-R interval dispersion.[31] It may not be solely dependent on the mean ventricular frequency since the median ventricular rate in humans is slower than in dogs (Figure 5), while their coefficient of variation is about equal. It is true though that we did not study this aspect systematically.

Size of the AV Node

If the shortest R-R intervals during atrial fibrillation as revealed by the histogram represent the shortest functional refractory period (FRP) of the AV conduction system, we may note that the FRP increases by a factor of 2 to 3, going from the dog, to man, to the horse. The same is true for the increase in median R-R interval during atrial fibrillation in dogs, humans, and horses (Figure 5). This increase, however, is small compared to the difference in sizes of the species. One may assume that the atrial excitatory process during atrial fibrillation is more or less the same in canines, humans, and horses because the respective monophasic action potentials of atrial cells do not differ by more than a few millivolts.[38] Similarly, the myocardial cells in all mammalian species are approximately the same size.[39] This probably justifies the conclusion that the difference in ventricular rate among dogs, humans, and horses during atrial fibrillation is due to a difference in AV nodal function. In addition, in the horse, during the long R-R intervals the autonomic nervous system seems able to influence AV conduction.

Although the AV node increases in size with an increase in body mass, this probably does not account for the increase in the median ventricular interval during atrial fibrillation in dogs, humans, and horses (Figure 5). The hearts of all mammals weigh roughly 0.6 percent of total body weight,[40] and the size of the AV node is roughly related to the size of the heart. If the size of the AV node as such were of paramount importance, a horse of 800 kg should theoretically have a median R-R interval during atrial fibrillation of at least 10 times as long as that in a man weighing 80 kg. Since this is evidently not the case, it may be assumed that in larger mammals the delaying function of the AV node diminishes.[41] According to this reasoning, the number of delaying cells per cubic millimeter in the equine AV node must be considerably fewer than in the human or canine AV node. However, their absolute number is probably still large enough to cause a net increase in the median R-R interval and especially in the longest R-R intervals. When more delaying cells are available and/or active at a given number and quality of atrial impulses, more concealment and longer R-R intervals will result.

SUMMARY

Comparative studies of ventricular rhythm patterns during atrial fibrillation in canines, humans, and horses allow for a concept that can explain similarities and differences between the species studied to date. These studies may also offer an explanation for the action of most drugs in atrial fibrillation and may shed some light on the R-R interval behavior during exercise and during conduction via a bypass tract.

In dogs and humans with atrial fibrillation the ventricular rhythm is random with a positively skewed histogram. The atrial excitatory process during atrial fibrillation is most likely a random process in itself. In dogs and humans, adaptation of AV conduction to atrial rate changes is too rapid to impose an effect on the ventricular rhythm. In humans, R-R intervals of over 2 seconds during atrial fibrillation hardly if ever occur, and therefore the autonomic nervous system cannot interfere

with the random pattern of the ventricular rhythm. The long R-R intervals in the horse probably cause autonomic neural interference with AV node conduction, and this may explain why the ventricular rhythm shows nonrandom patterns. The difference in ventricular rates and rhythms during atrial fibrillation in dogs, humans, and horses are small considering the differences in body weights and thus the heart sizes. The number of actually available or active cells in the AV node and the refractory period of the AV system are probably responsible for the differences in median R-R intervals in the species studied. Most drugs that affect R-R interval behavior during atrial fibrillation do so by a combined effect on the atrial myocardium and the AV conduction system.

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