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Heart and Vessels

Comparative study of atrial fibrillation and AV conduction in mammals

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Summary. Atrial fibrillation is one of the most common cardiac arrhythmias in humans. It also occurs quite frequently in dogs and horses. Comparative study of this arrhythmia may contribute to better understanding of the pathophysiological mechanisms involved.

In this study, we present a quantitative analysis of atrial fibrillation in humans, dogs, horses, and in a kangaroo, making use of histograms and serial autocorrelograms of the ventricular rhythm with and without digitalis medication.

Increase in the size of the animal and thus in the size of the heart is accompanied by a decrease in ventricular rate. The ventricular rhythm was random in the dog, kangaroo, and man, but periodicity was present in the horse. Digitalis decreased the ventricular rate in all species studied and enforced the periodicity in the horse.

The differences in the atrial excitation process, atrioventricular (AV) conduction, and ventricular behavior between the four species studied are small when compared with the differences in their heart size.

We conclude that in evolution, as far as the heart is concerned, cell size and morphology probably prevail over cell-function.

Introduction

Comparative medicine may contribute to a better understanding of human and animal physiology and pathology. In this regard, one field that seems quite promising is the comparative study of rhythm and conduction abnormalities; atrial fibrillation certainly presents itself as an arrhythmia that is suitable for comparative study. Atrial fibrillation is one of the most common cardiac arrhythmias in humans [1, 2]. Its incidence increases with increasing age and tends to be related to myocardial disease, such as coronary artery disease, hypertension, mitral stenosis, and hyperthyroidism. In the Western hemisphere and probably also in Japan, atrial fibrillation in humans is mainly caused by coronary heart disease [2–5].

It is of interest that atrial fibrillation is also not infrequently observed in domestic animals that reach an advanced age like dogs and horses [6–13]. One would also expect to encounter atrial fibrillation in mammals larger than dogs in zoos, because these animals can also reach a considerable age. As an example of this, we observed atrial fibrillation in a kangaroo in a zoo in Bristol, England. A systematic electrocardiographic study of large and old mammals in our zoos would probably reveal quite a number of cases with atrial fibrillation and/or other arrhythmias.

Veterinarians are well aware of the frequent existence of atrial fibrillation in dogs and horses, but in cattle it is quite rare [14, 15]. Another feature of atrial fibrillation is that it is hardly ever observed in smaller animals like cats, rabbits, and rats [12]; also, in dogs less than 20 kg body weight it does not seem to occur [11]. Atrial fibrillation is seldom seen in infants, children, and young adults. This can easily be explained by Moe's multiple wavelet theory [16–18]. Atrial fibrillation is a well-known arrhythmia in large dogs, humans, and horses with advanced age and/or large hearts.

In this paper, we report on our studies on spontaneous atrial fibrillation in dogs, a kangaroo, humans, and horses. The goal of our study was to gain further insight into the mechanism of the arrhythmia itself, the role of the atrioventricular (AV) junction during atrial fibrillation, and to analyze the effect of digitalis and the influence of the autonomic nervous system.

Methods

We studied spontaneous atrial fibrillation in dogs, a kangaroo, humans, and horses, making use of quantitative analysis of

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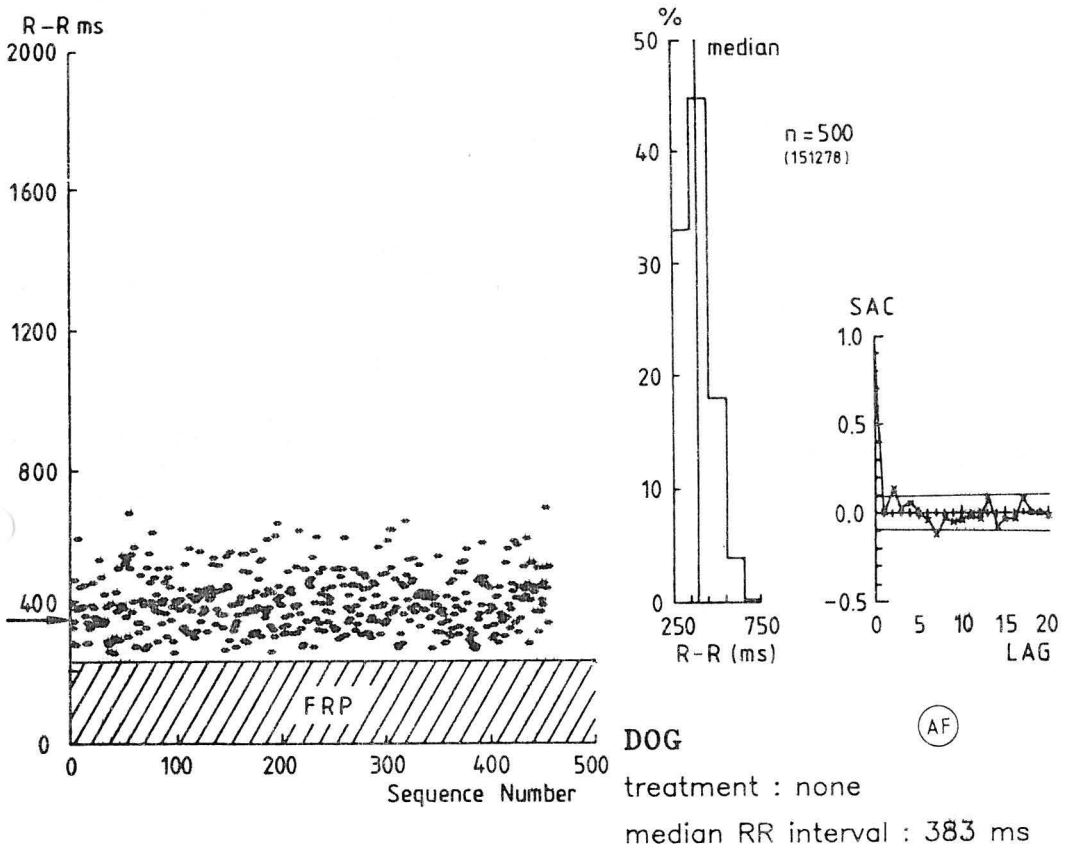

Fig. 1. Interval plot, histogram, and serial autocorrelogram (SAC) of a dog with atrial fibrillation (AF). *FRP* functional refractory period. The *arrow* indicates the median RR interval

the ventricular rate and rhythm. The ECGs were recorded on magnetic tape using the extremity leads. The tallest R waves were used for QRS detection and computation of the RR intervals. Interval plots, histograms, and serial autocorrelograms (SAC) were derived from a series of about 500 consecutive RR intervals. The computational methods we used have been described in detail in previous publications [19–21]. Essentially the same technique was employed in all species.

ECG recordings from dogs were obtained either during superficial anesthesia or, whenever possible, while the animals were fully conscious and lying on their sides. In humans, the ECGs were always recorded in the supine position under steady-state conditions in a temperature-controlled room. The ECGs in horses were obtained while they were standing quietly in their stables. The ECG of the kangaroo was recorded while the animal was sitting in its enclosure in Bristol Zoo (England). The kangaroo was about 15 years of age.

In dogs with atrial fibrillation, the ECGs were recorded before and during digitalis treatment; in humans, the effect of exercise, digitalis, quinidine, and verapamil was tested; in horses we recorded the ECGs before and during digitalis, quinidine, and atropine treatment. In recent years, we have performed our study in ten dogs, one kangaroo, numerous humans, and eight horses.

Results

We present here data from untreated humans and animals as well as the results of the effect of digitalis on ventricular rate and rhythm. In Fig. 1, the interval plot, histogram, and SAC of a representative untreated dog with atrial fibrillation are shown. It can be seen that the shortest RR intervals are in the order of 200 ms. The functional refractory period (FRP) of the AV conducting system is represented by the shaded bar in the interval plot. The longest RR intervals have a duration of 600–700 ms. The median RR interval is 383 ms. The histogram is positively skewed and the SAC indicates that the ventricular rhythm is random.

Figure 2 demonstrates the same computed data from the kangaroo. The FRP, represented by the shortest RR intervals [22], is slightly longer than in the dog. The long RR intervals are in the order of 1200–1500 ms. The longest interval is 2270 ms. The median RR interval is 532 ms. As in the dog, the histogram is positively skewed. The SAC demonstrates that the ventricular rhythm in the kangaroo is also random.

The interval plot, histogram, and SAC of a representative untreated human patient with atrial fibrillation are shown in Fig. 3. The FRP of the AV conducting system is 400 ms and the longest RR intervals reach values of 1200–1500 ms. The median RR interval is 712 ms. The histogram is skewed. The SAC shows that the ventricular rhythm during atrial fibrillation in man is random.

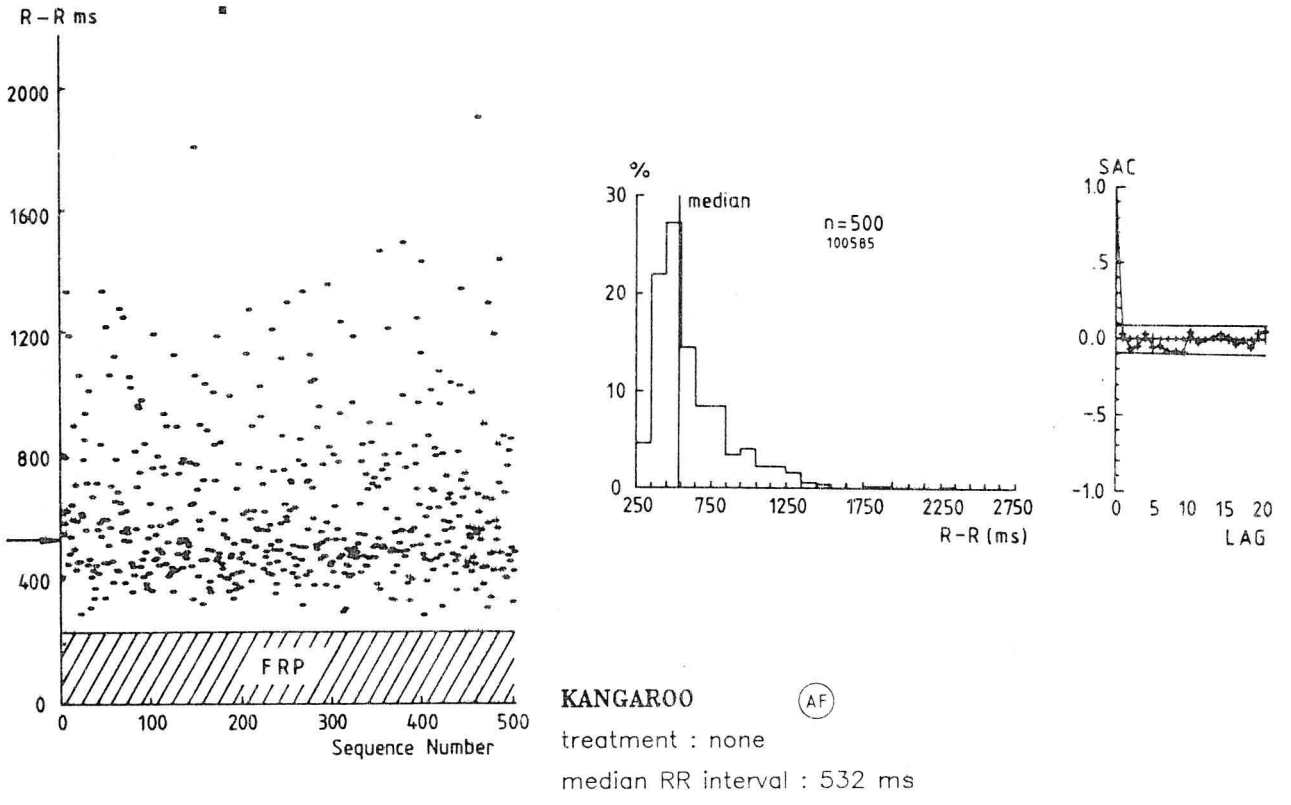

Fig. 2. Interval plot, histogram, and serial autocorrelogram (SAC) of a kangaroo with atrial fibrillation (AF). *FRP* functional refractory period. The *arrow* indicates the median RR interval

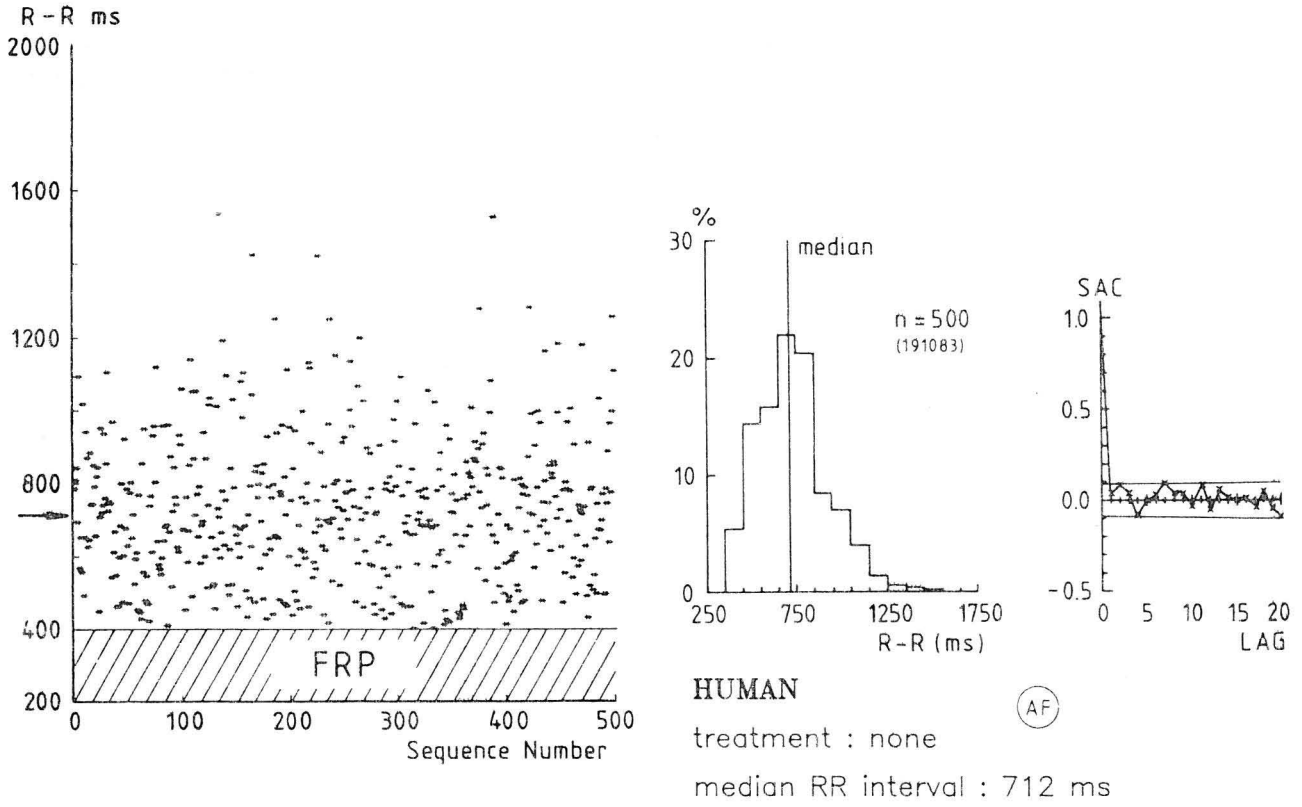

Fig. 3. Interval plot, histogram, and serial autocorrelogram (SAC) of a human with atrial fibrillation (AF). *FRP* functional refractory period. The *arrow* indicates the median RR interval

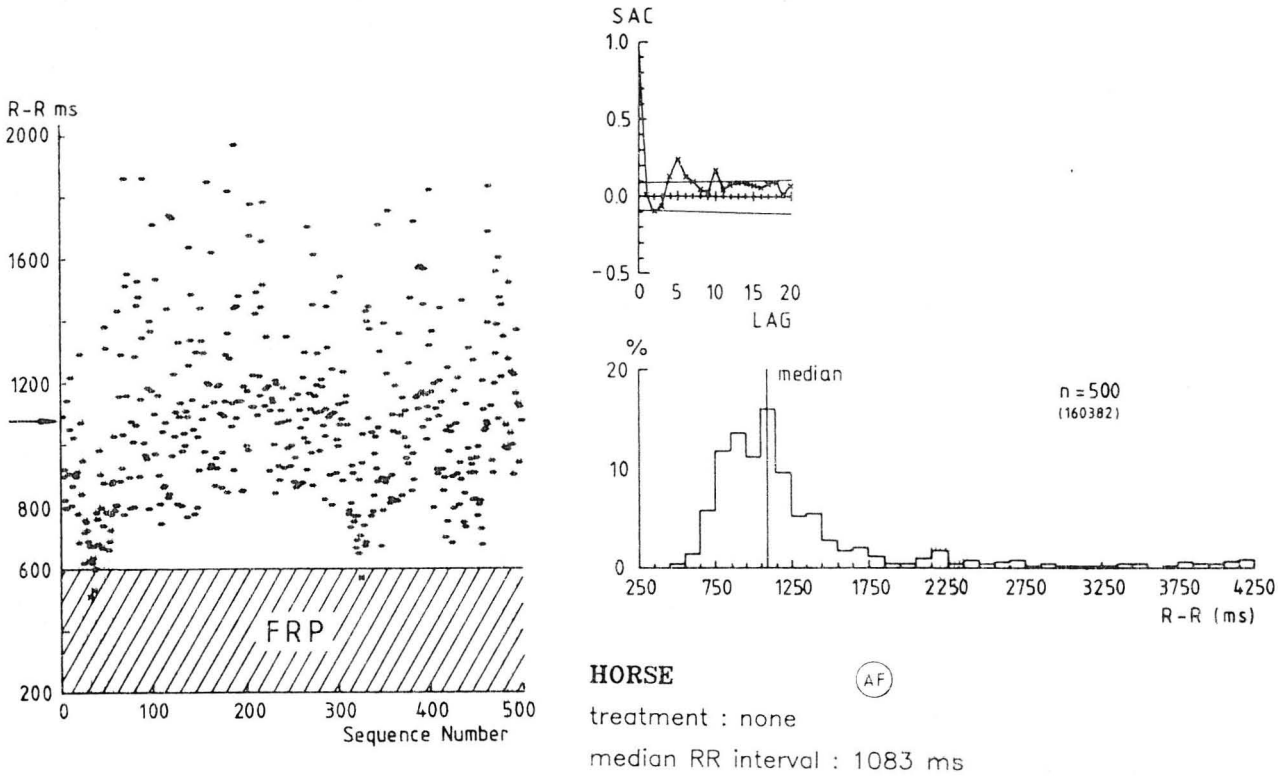

Fig. 4. Interval plot, histogram, and serial autocorrelogram (SAC) of a horse with atrial fibrillation (AF). *FRP* functional refractory period. The *arrow* indicates the median RR interval

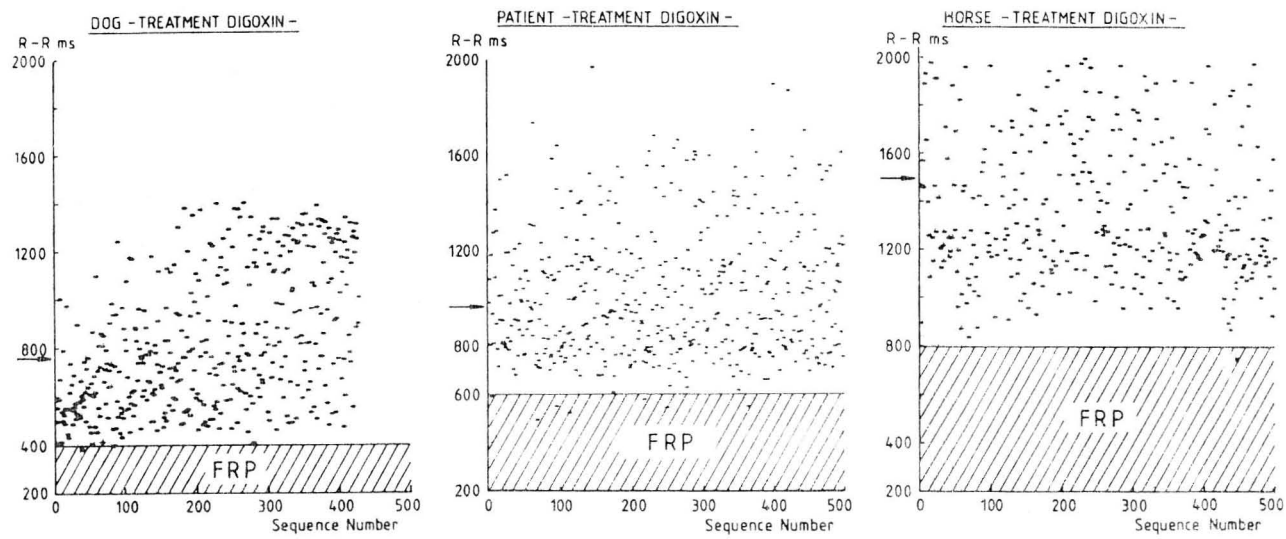

Fig. 5. Interval plots of the ventricular rhythm during atrial fibrillation and digitalis treatment of a dog, a human patient, and a horse. The *arrow* indicates the median RR interval. For further explanation, see text

The horse shows a slightly different pattern (Fig. 4). In the interval plot of a representative horse, it can be seen that short and long RR intervals tend to cluster. Intervals longer than 2000 ms are not shown. The FRP is in the order of 600 ms. The histogram is quite skewed and shows clearly that RR intervals may reach values of over 4000 ms. The median RR interval is 1083 ms. The SAC shows a distinct tendency toward periodicity; in other words, in horses with atrial fibrillation the ventricular rhythm is not random.

In Fig. 5, the interval plots of the ventricular rhythm during atrial fibrillation and treatment with digitalis are shown from left to right in the dog (cf. Fig. 1), the human patient (compare Fig. 3), and the horse (compare Fig. 4). It should be noted that in addition to the lengthening of the FRP and the median RR intervals due to digitalis, the number of

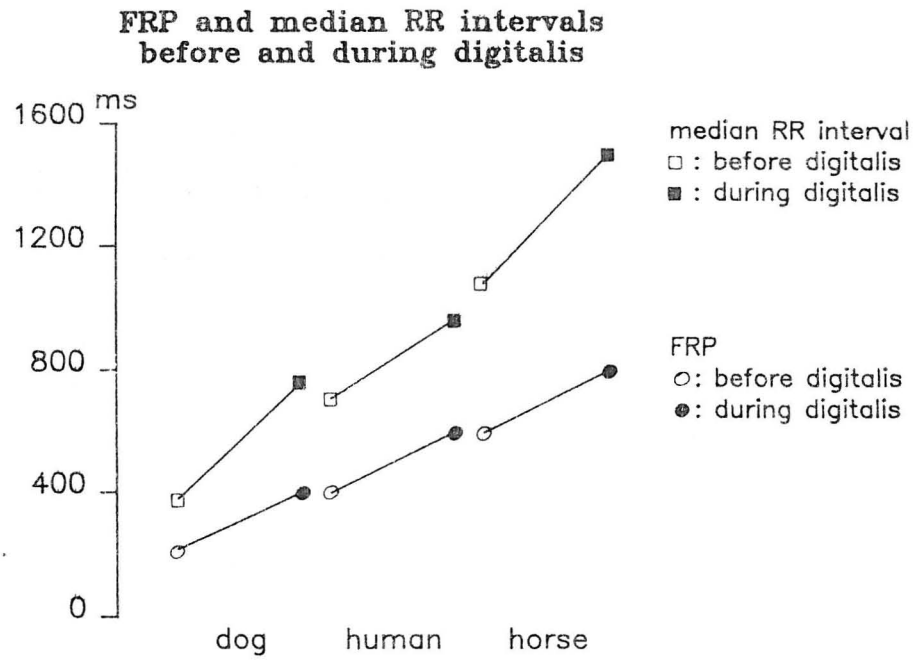

Fig. 6. Median RR intervals and FRP of a dog, human, and horse with atrial fibrillation before and during digialis treatment. It can be seen that digitalis causes the dog values to be similar to those of a human patient without digitalis and the human values to be similar to those of a horse without the drug

long intervals has increased. Considerably higher values of RR intervals are obtained. The periodicity in horses becomes more pronounced (not shown).

In Fig. 6, the median RR intervals and the FRPs are shown in the dog, man, and horse before and during digitalis treatment. There is a shift toward higher values.

Discussion

The differences between the ventricular rate and rhythm in dogs, humans, and horses with spontaneous atrial fibrillation are small compared with their body weight (Table 1). The heart weight in all mammals is close to 0.6% of the body weight [23] and, as shown by Prothero [24], the relation between heart weight and body weight is amazingly constant with a correlation coefficient of 0.98. There are no quantitative studies on AV nodal size versus heart weight, but the impression obtained from comparative studies is that the size of the AV node increases more or less linearly with the size of the heart. At the same time, specific nodal cell density seems to diminish with an increase in nodal size. There is a relative increase in the connective tissue between typical nodal cells (TN James, personal communication).

Table 1. Atrial fibrillation

	Dog	Man	Horse
weight (kg)	20	70	750
median RR interval (ms)	300	600	1000
ventricular rhythm	random	random	periodicity

Although the differences between ventricular rate and rhythm in dogs, humans, and horses with atrial fibrillation are small (given their differences in size) they are definitely present [25]. The first question is why should this be so? Can it be explained on the basis of differences in the atrial fibrillation process as such, is it caused by differences in AV junctional behavior, or by a combination of these two factors? In this respect, it is of interest that digitalis changes the ventricular rate and rhythm of a dog with atrial fibrillation into a pattern quite similar to that of a human without digitalis treatment [26]. At the same time, human patients with atrial fibrillation receiving digitalis treatment have an FRP that comes close to that of horses without digitalis [10]. The effect of digitalis seems to make the AV node bigger. Digitalis slows AV conduction [27] and has a twofold action on the atria: It affects the atrial myocardium both directly and by its vagal action [28, 29].

Can the atrial electrical activity during atrial fibrillation in dogs, humans, and horses be expected to differ substantially? The monophasic action potential (MAP) of the mammalian atrial myocardium in the species studied so far is quite similar in voltage, form, and duration [30]. If the MAP of the atrial myocardium of a rat and dog, for instance, hardly differ, why should the MAP of human atrial myocardium be different from that of equine atrial myocardium? As a first approximation, it seems fair to assume that there are no major differences between the excitation process during atrial fibrillation in the dog, man, and horse.

AV conduction times as expressed by the PR interval in the ECG of dogs, humans, and horses do not differ too much; in the dog the conduction time is between 100 and 150 ms, in the adult human between 150 and 200 ms, and in the horse between 250 and 350 ms [31]. The PR interval includes the time required to traverse the AV junction as well as the conduction time through the His-Purkinje system. It may be assumed from the similarity in His bundle fiber diameter that the conduction velocity in the His-Purkinje system in the dog, human, and horse will be approximately the same—2.5 m/s [32, 33]. So, the relative contribution to the AV conduction time of the His-Purkinje system increases with the size of the mammal with the consequence that AV nodal delay in the horse must be relatively shorter than in man or the dog.

Assuming a similar atrial excitation process during atrial fibrillation in dogs, humans, and horses and only a small increase in AV nodal delay, the differences in ventricular rate between these three species must be accounted for by: (1) the increase in FRP [22], but above all by (2) the increase in concealed conduction [34, 35].

The capacity for concealed conduction during atrial fibrillation expresses itself in the number and duration of the longest RR intervals, which increase considerably from the dog through man to the horse. This increase also occurs during digitalis treatment. Similar phenomena need not be due to similar causes. In the case of equal number and quality of atrial impulses, the degree of concealment is probably related to the number of conduction elements in the AV junction. At a constant AV nodal size and, thus, a constant number of nodal cells, the degree of concealment can be enhanced by an increased number of atrial excitatory impulses like during digitalis treatment. Smaller AV nodes impose a relatively long delay but have less capacity for concealed conduction. Larger AV nodes cause a relatively short delay but have a greater capacity for concealment. The ventricular rate and its long/short RR intervals ratio during atrial fibrillation is a trade-off between the quality and number of atrial excitations and the capacity for concealment in the AV node. In this reasoning, we make use of the classic concept of FRP and concealed conduction as the basic mechanisms to explain ventricular rate and rhythmicity during atrial fibrillation [34, 35]. However, there is evidence [36] that this classic concept cannot explain a number of features such as the effect of ventricular pacing or ventricular extrasystoles on AV conduction and the ventricular rhythm in atrial fibrillation.

A group of cells in the AV junction acting as a nonprotected pacemaker with random electrotonic modulation of the phase 4 slope and duration offers an unrestricted explanation for nearly all aspects of ventricular rhythmicity during atrial fibrillation [36].

This also raises the aspect of randomness of the ventricular rhythm during atrial fibrillation. It is generally accepted that the random ventricular rhythm during atrial fibrillation is caused by the erratic atrial rhythm itself [37, 38]. The number of atrial impulses arriving per unit of time at the AV junction follows a Poisson distribution [36, 40]. Whether the AV junction acts as a filter in the classic concept or as an unprotected pacemaker, the cause for the random pattern of the ventricular rhythm has to be looked for in the atrial rhythm [20]. We have collected evidence to explain why in dogs and humans the ventricular rhythm is random and why in horses it is not [39]. In horses, the long RR intervals cause a considerable drop in blood pressure, which in turn may cause autonomic nervous interference with the AV conduction properties [10]. In dogs and humans, RR intervals during atrial fibrillation seldom exceed 2000 ms, which is probably too short for the autonomic nervous system to interfere with the conduction of atrial impulses, and therefore the ventricular rhythm is random.

If indeed the atrial excitatory process during atrial fibrillation in dogs, humans, and horses is more or less identical, the differences in ventricular rate and rhythm must reside within the AV junction. The functional differences, however, are small when compared with the heart size and, thus, the size of the AV node. This implies that given the identical size and in spite of the similar morphology of mammalian AV nodal cells, the functional difference for each cell must be considerable.

Conclusion

The functional differences between the AV junctions of dogs, humans, and horses during sinus rhythm and atrial fibrillation are small taking into account the dimensions of their respective hearts. Cell size and architecture of the heart are fairly constant in all mammals [40, 41]. Small functional differences in different hearts despite their large dimensional differences can therefore only be explained on the basis of considerable differences in the function of the individual heart cells.

The question of archetype versus adaptation has recently been discussed by Gould [42]. It was a matter of great intellectual challenge to Goethe, Darwin, Russell, and other scientific giants; so it would be difficult for a humble cardiologist to provide a definitive answer. We would seek it today in the universal structure of genetic material, in the blueprint of DNA. However, considering the similarity in the micro- and macroarchitecture of the heart and

the minute functional differences in AV junctional behavior as a whole among different mammalian species with great differences in the size of the animals, one would be inclined to regard archetype as primary and adaptation as secondary in mammalian evolution. With the same cell-size and -morphology function per cell may differ considerably.

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Discussion after the presentation by Dr. Meijler

Watanabe: I wonder if you looked at the frequency of f waves in these animals? Does the size of the right atrium or the entire atria affect the frequency of the f waves rather than the RR intervals?

Meijler: I have not studied that, but from the data I received this morning, except for those presented of the cat, it was my impression that the frequency of f waves in dogs, horses, and humans is approximately the same. In form and duration of the monophasic action potential, dogs, humans, and horses are also not too different. So, I would expect that the atrial fibrillation process in these species may not be identical but quite similar and not enough to explain the differences in ventricular rate. When digitalis is given, a decrease in ventricular rhythm is obtained and it is mainly caused by the increase in the number of f waves that reach the AV junction; this will give increased concealed conduction. Since it can be blocked by atropine, it is said that digitalis has a vagal effect. I am not sure that this is true.

Also, you have seen this morning in some of the presentations in which the effect of quinidine has been shown that before quinidine turns atrial fibrillation into sinus rhythm there is an increase in ventricular rate, which is because the atrial rate is slowed and less concealed conduction is obtained. So, my answer is that I think it is about the same.

Watanabe: Of course, in the case of quinidine administration, in addition to what you mentioned about the slowing of atrial fibrillation, there is the anticholinergic action, which could enhance AV nodal conduction. Regarding the difference between the number of concealments in these animals and the great variations in size, do you think that such an increased number of concealments in larger animals like horses is dependent on the anatomical structure, as you have shown that in larger animals the AV nodal fibers are much more sparse than in humans or smaller animals? Could this affect the degree of concealed conduction? There may also be structural differences in the junction of atrial tissue and AV nodal fibers between different animals.

Meijler: I think this is so. I would hypothesize that the number of specific nodal cells per volume unit of AV node decreases from the dog to man to the horse. Although the total number of AV nodal cells is larger in man than in the dog, it is not in proportion. If it were in proportion, the RR interval in dog would be much longer. So, I believe the situation is exactly as you said, but I think that real quantitative morphometric studies should be done. Drs. James and Kawamura are looking into this in the whale, horse, and dog.

Sugishita: You showed us a slide of a kangaroo. Have you studied many kangaroos? I am interested in the hearts of kangaroos and I have recently studied the electrocardiograms of about ten kangaroos in Australia. I found that the QT interval was very short in most animals. The QT interval in your slide was also short. Have you any ideas about that?

Meijler: No, I am interested in comparative atrial fibrillation and I received a letter from a veterinarian in Bristol in England saying that he had a kangaroo with atrial fibrillation. He asked me whether I was interested, so I sent a whole electrocardiology team over to Bristol to make a recording. This was my single experience with the kangaroo. The problem of QRS, QT interval, and T wave is fairly complicated and is dependent to a large extent on the distribution of the Purkinje system. I only know that in horses and cattle there is an endocardial to epicardial distribution of Purkinje fibers; I do not know about the Purkinje system in kangaroos. The Purkinje fibers have to be studied in order to obtain a better insight into the QT interval and T wave.

Murao: What do you think about the influence of body temperature on the conduction time?

Meijler: The temperature of all mammals is between 36° and 38°C. There is an excellent book by Dr. Schmidt Nielsen of Duke, and he looked at all different aspects of biological signals in different animals. One of the things that is amazingly constant in all mammals is body temperature. So, body temperature cannot explain the differences in heart rate.