Nonrandom Ventricular Rhythm in Horses With Atrial Fibrillation and Its Significance for Patients

FRITS L. MEIJLER, MD, FACC,* JAN KRONEMAN, DVM,† INGEBORG van der TWEEL,*
JOHAN N. HERBSCHLEB, MSc,* ROBERT M. HEETHAAR, PhD,* CORNELIUS BORST, MD*

Utrecht, The Netherlands

RR interval sequences during spontaneous atrial fibrillation in eight horses were analyzed as in previous studies in patients and dogs using histograms and serial autocorrelograms. In patients and dogs with spontaneous atrial fibrillation, ventricular rhythms were always random. In the horses, the histograms were skewed with median RR intervals of approximately 1,000 ms. A striking finding in these animals was the presence of long RR intervals up to 5,000 ms in duration. The shortest RR intervals lasted 400 to 600 ms. In contrast to findings in dogs and patients, the serial autocorrelograms showed periodicity that was reenforced by digitalis (n = 3), but eliminated by quinidine (n = 2) and atropine (n = 2). Quinidine and atropine eliminated the longer RR inter-

vals, whereas digitalis increased the number of long RR intervals.

In one horse, it was possible to measure intraarterial pressure, and large fluctuations in pressure were observed as the RR intervals varied from over 3,000 to less than 500 ms. It is postulated that these changes in blood pressure are associated with baroreceptor responses that may alter the electrophysiologic behavior of the atria and atrioventricular node. These changes cause the nonrandom patterns of ventricular rhythm in the horse. Because such very long RR intervals do not occur in human beings or dogs during atrial fibrillation, the random ventricular rhythm in these groups is maintained even during digitalis treatment.

We have previously (1–4) stressed that the ventricular response during spontaneous atrial fibrillation in patients and dogs is random. We found that neither digitalis, exercise nor quinidine affected the randomness of the ventricular rhythm in patients with atrial fibrillation. We concluded (2) that the inherent atrial excitatory process in atrial fibrillation had to be a random phenomenon and that atrial impulses reach the atrioventricular (AV) junction from random directions, with random strength and at random intervals. By means of such mechanisms as refractory period (5,6) and concealed conduction (7–9) the AV node scales down the frequency of transmission of the atrial impulses causing the ventricle to beat at a rate considerably lower than that of the atrium. This conclusion was later confirmed by Billette et al. (10), who found that in well established atrial fibrillation in dogs, the degree of ventricular irregularity (dispersion of RR intervals) is related to the conductivity in the

AV junction while the random character of RR interval sequences is related to the atrial fibrillatory activity itself.

In other studies (11) we found that adaptation of AV conduction time to atrial rate and atrial interval changes in rats, dogs and human beings appeared to be time-dependent rather than rate-dependent. AV conduction in the presence of well defined atrial rhythms adapts quickly to changes in intervals between conducted AA (PP) intervals; that is, AV conduction has a short time constant or memory (12–16). We reasoned that this short memory, lasting about one or two cycles in human beings, may also be applicable to AV nodal behavior during atrial fibrillation. The short memory of the AV node cannot impose a long-term effect on the random sequence of the conducted atrial impulses. For this reason during atrial fibrillation in patients and dogs, the random pattern of atrial excitation is transmitted to the ventricle at the aforementioned scaled down rate. Comparison of AV conduction properties in rats, dogs and human beings (11,15,16) indicates that as heart size and, thus, AV nodal size increase, the AV nodal "memory" becomes relatively shorter.

Because horses have a large heart and often have atrial fibrillation (17,18), we elected to study these animals as the next step in our comparative pathophysiologic studies of

AV nodal behavior during atrial fibrillation. However, our group is not the first to study atrial fibrillation in horses to obtain a better understanding of what is happening in human beings. As early as 1912, Lewis (19) stated, "Towards the termination of the observations made upon complete irregularity of the heart's action in the human subject, . . . , it occurred to me that if I could find a similar pathological affection in any of the lower animals, it might finally *settle* (italics are ours) the nature of the irregularity with which I had to deal."

Methods

Study animals. Eight horses (Table 1) with atrial fibrillation referred to the Clinic for Large Animal Medicine of the Veterinary School at the University of Utrecht were studied. They had no other apparent diseases. The Veterinary School in Utrecht is the only one in the Netherlands and accepts animals referred by veterinarians in the country.

Recordings. The electrocardiograms were recorded on magnetic tape using the limb leads while the horses were standing quietly in their stable. Each tracing was approxi-

mately 20 minutes in length and allowed for about 1,000 RR intervals that were necessary for acceptable data analysis. The lead presenting the tallest R waves was selected for QRS detection and computation of RR intervals. Histograms and serial autocorrelograms were produced by digital computer using essentially the same procedure as described in detail in our earlier studies dealing with the analysis of irregular ventricular rhythms in patients (2) and dogs (4).

Drug studies. In three horses, an electrocardiogram was taken before and after digitalis administration in doses of 0.02 mg digoxin/kg given in a neck vein. Another two horses were studied before and during quinidine administration of 400 and 800 ml 2% quinidine-gluconate intravenously, while in two more horses an electrocardiogram was recorded before and immediately after intravenous injection of 25 mg atropine. The electrocardiogram of one horse that received quinidine could not be analyzed, because the horse developed ventricular tachycardia. The effect of this intervention was omitted from Table 1.

Blood pressure and pathologic studies. To further explain the results of the analysis of the ventricular rhythm, we were able to record intraarterial blood pressure in one

Table 1. Data on the Eight Horses

| Horse | Age (yr) | Weight (kg) | Episode | Treatment | RR Interval | | | |
					No.	Range (ms)	Median (ms)	Periodicity*
1 (8202067)	16	648	1	None	1,000	(358 to 4,595)	1,233	4
2 (8201157)	7	657	1	None	989	(468 to 4,118)	1,108	5
			2	Quinidine (up to 800 ml, 2%, IV)	874	(290 to 1,428)	548	—
			3	None	995	(477 to 3,362)	914	5
			4	Digoxin (0.02 mg/kg IV)	1,000	(368 to 3,454)	992	4 to 5
3 (8203134)	10	530	1	None	662	(633 to 4,898)	1,258	4
4 (8203151)	6	512	1	None	997	(489 to 5,319)	1,064	5
			2	Digoxin (0.02 mg/kg IV)	617	(749 to 5,873)	1,502	3 to 4
5 (8203238)	12	632	1	None	778	(471 to 4,398)	932	4
6 (8204205)	4	402	1	None	995	(588 to 3,057)	948	4 to 5
7 (8209138)	4	379	1	None	427	(699 to 5,181)	1,314	4 to 5
			2	Atropine (25 mg IV)	742	(639 to 3,003)	1,085	—
8 (8303155)	8	546	1	None	1,000	(485 to 1,396)	718	—
			2	Atropine (25 mg IV)	1,000	(470 to 1,297)	667	—
			3	None	999	(508 to 1,533)	763	—
			4	Digoxin (0.02 mg/kg IV)	1,000	(547 to 1,535)	854	—

*Periodicity in the serial autocorrelogram as indicated by the number of coefficients. In Horse 2, intraarterial blood pressure was recorded. Horse 8, which had to be killed, did not react to digitalis and also manifested ventricular tachycardia after the administration of quinidine. See text for details. IV = intravenously.

horse (Horse 2, Table 1). After local anesthesia but without any premedication, a catheter was inserted in one of the forelimb arteries. Blood pressure was recorded using a standard transducer. One horse (Horse 8, Table 1) had to be killed because the heart failure could not be controlled. The heart was dissected for spatial reconstruction of the AV node and these studies are ongoing.
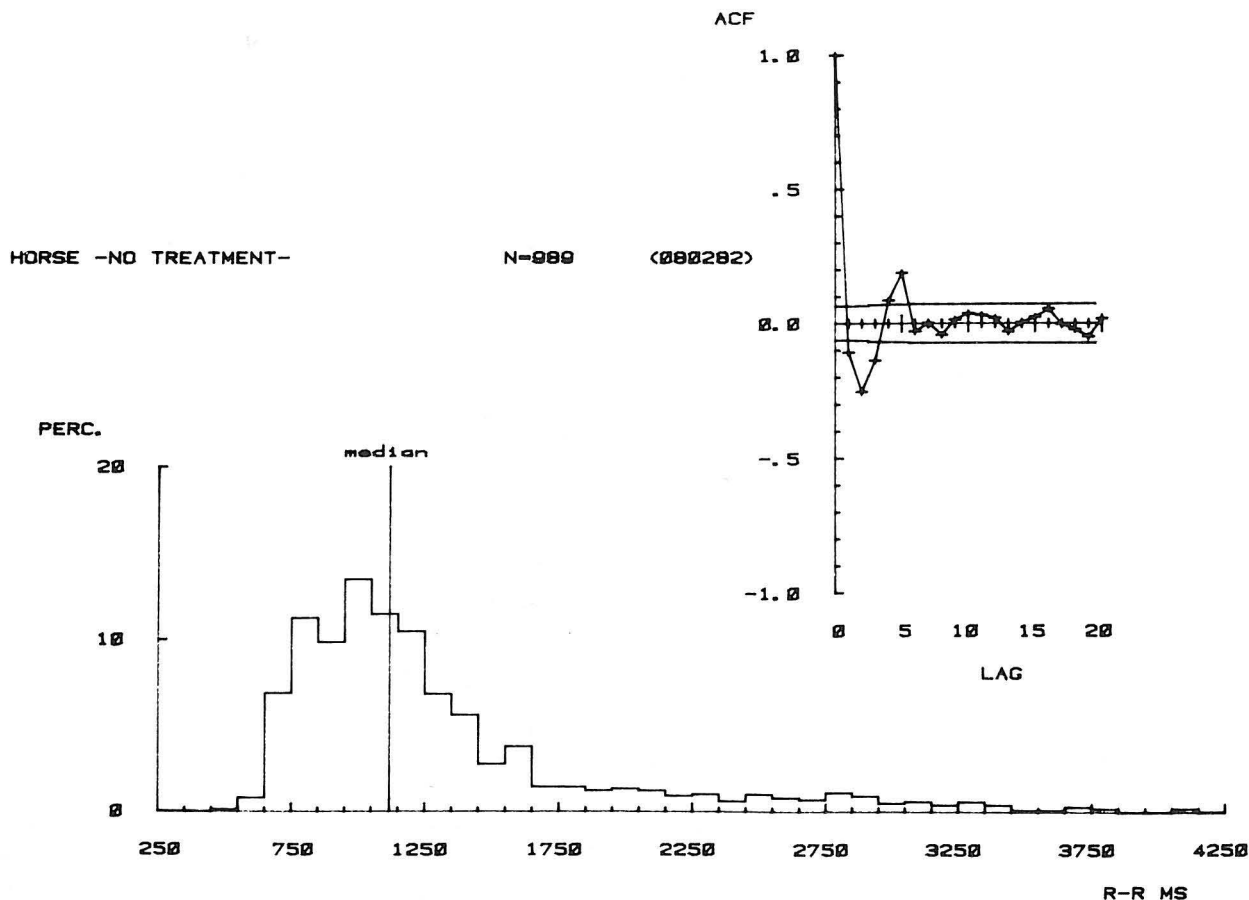
Results

The histograms and serial autocorrelograms of all eight horses with untreated atrial fibrillation showed a more or less similar pattern. The histogram in Figure 1 is quite skewed with a large difference between the shortest and the longest RR intervals (median about 1,000 ms). The duration of the short intervals (400 to 600 ms) is considered to represent the functional refractory period of the atrioventricular (AV) junction (20). The long intervals reach durations of close to 5,000 ms. The serial autocorrelogram shows a tendency to periodicity. In general, very long RR intervals are followed by four to five RR intervals of short duration (Fig. 2). Digitalis lengthens the RR intervals and increases the periodicity of RR intervals as shown in the serial autocorrelograms (Fig. 3). This is associated with an increase in
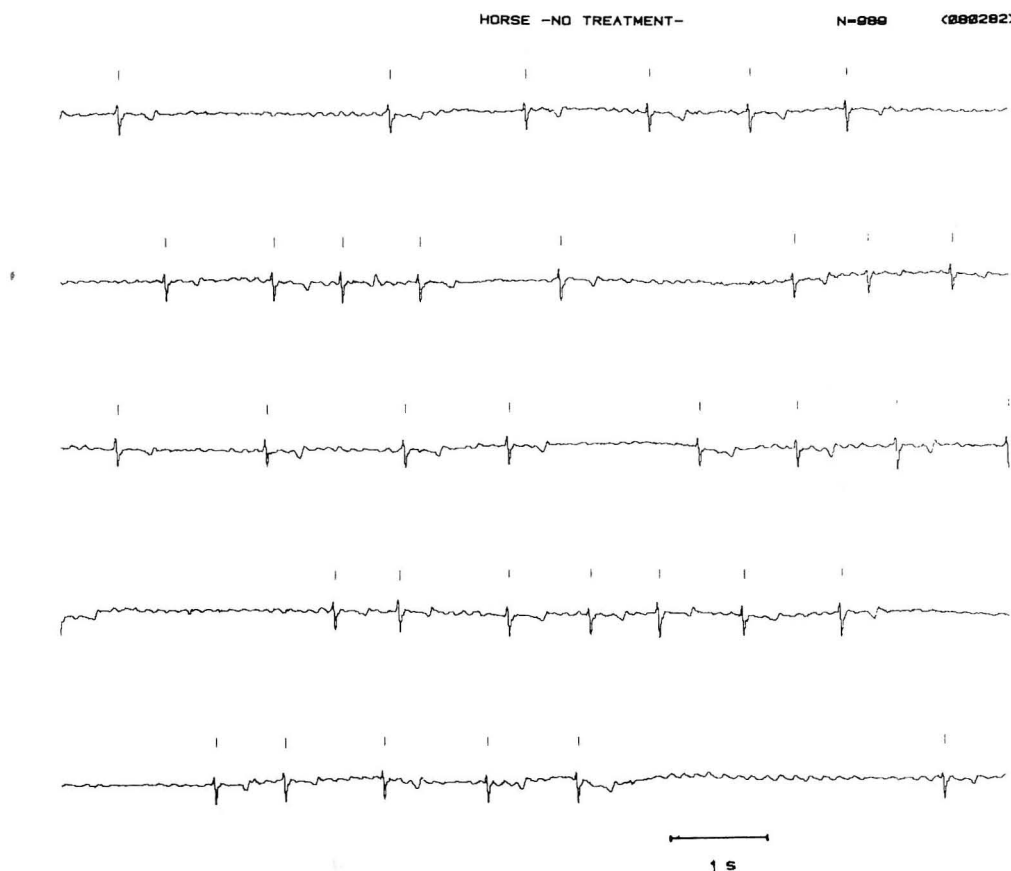
the number of RR intervals longer than 4,500 ms. Quinidine and atropine have an opposite effect (Fig. 4). The median RR interval is shortened, the very long intervals disappear thereby altering the histograms and serial autocorrelograms. The minimal RR interval, reflecting the functional refractory period (20), shortens; the skewness of the histograms diminishes and all coefficients of the serial autocorrelogram, except the first, come within the 95% confidence limits. In other words, the ventricular rhythm becomes random as in patients and dogs. Figure 5 shows the intraarterial blood pressure recording in one horse. The systolic blood pressure decreases to 60 mm Hg during the long RR intervals.

Discussion

Previous concepts of random nature of ventricular rhythm in atrial fibrillation. This study is part of a com-

Figure 1. Histogram (**left**) and serial autocorrelogram (**right upper corner**) of Horse 2 (Table 1, episode 1). The **lines** horizontal to the x-axis represent the 95% confidence limits. Within those limits, the correlation coefficients are not statistically different from zero. For further details see text. ACF = autocorrelation function; LAG = coefficient number; MS = milliseconds; PERC. = percent.

Figure 2. Electrocardiographic record from Horse 2 (Table 1, episode 1) demonstrating the sequence of short and long intervals that produces autocorrelograms like that in Figure 1.
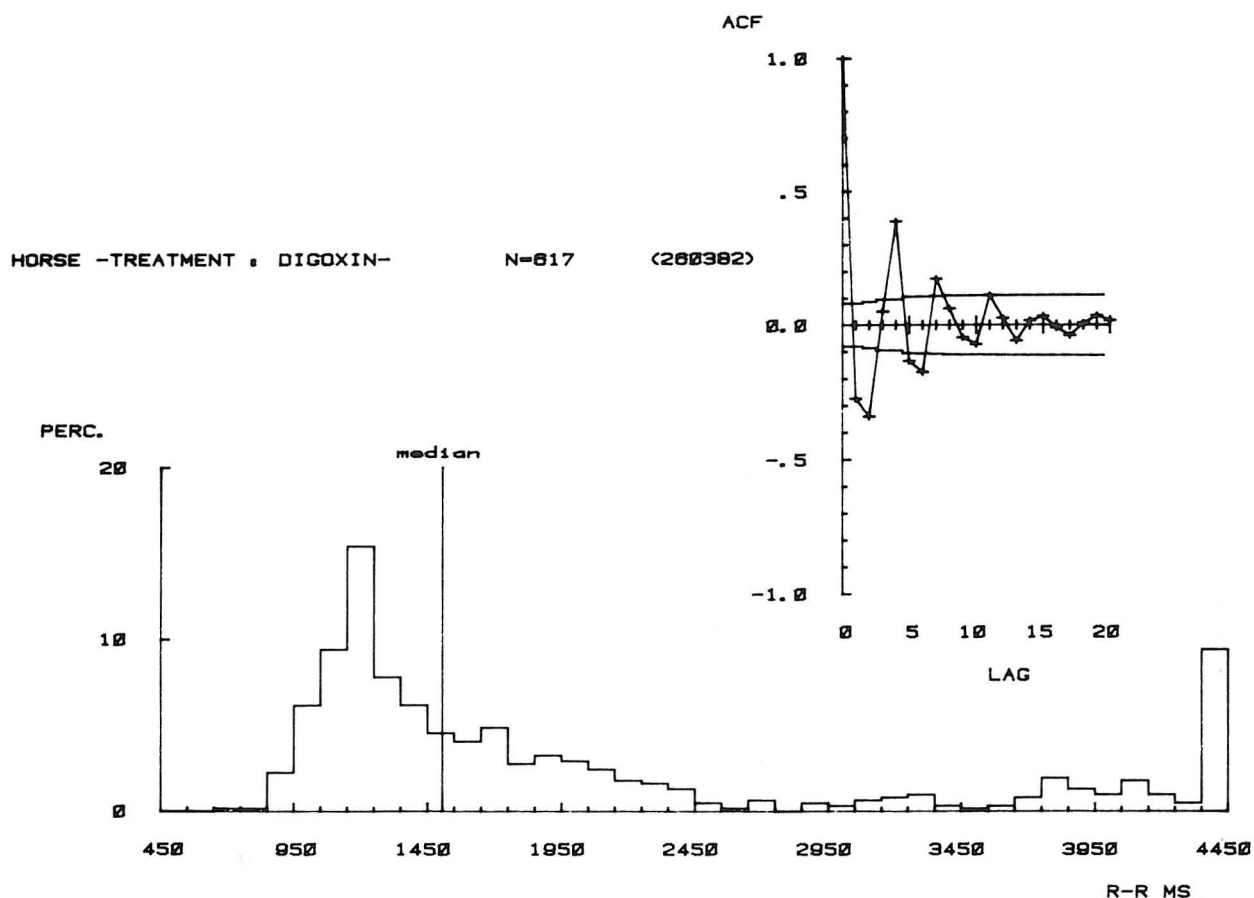
parative pathophysiologic project to investigate ventricular rhythm and AV junctional behavior during atrial fibrillation. The random ventricular rhythm found in patients with atrial fibrillation (2) was considered to be the result of a random excitation process in the atria. In dogs with spontaneous atrial fibrillation (4) we also found the ventricular rhythm to be random. During ventricular fibrillation with retrograde conduction, the atrial rhythm is also random (21). Similarly, in a patient with Wolff-Parkinson-White syndrome, the RR intervals were random regardless whether the AV conduction proceeded along the bypass or the AV junction (unpublished data). Rowland et al. (22) observed that in patients with an atriofascicular bypass tract or rapidly conducting AV node, there was no significant periodicity in the RR intervals during atrial fibrillation. This further strengthened the notion that the atrial excitation process in atrial fibrillation, indeed, had to be random and that the role of the AV node during atrial fibrillation is limited to scaling down the high atrial rate.

Role of AV node. These observations compelled us to study the effect of a variety of atrial rhythm patterns on AV conduction in human beings, dogs and rats (11,15,16,23). The conclusion from those studies was that AV nodal "memory" is too short to interfere with AV conduction, especially in the larger species. The AV node does not impose order on induced atrial random rhythms or contribute to it. Consequently, the ventricular rhythm in spontaneous atrial fibrillation remains random as well.

We also observed only small differences in AV conduction properties with changes in atrial stimulation patterns as compared with the relative sizes of the AV node in human beings, dogs and rats. Therefore, in horses, we expected to find random ventricular rhythms in response to atrial fibrillation as well. Our findings in horses, however, suggest that we originally oversimplified the scaling role of the AV junction or that our concept of the random atrial excitation pattern in atrial fibrillation was erroneous, or both.

Role of prolonged RR interval and arterial blood pressure in horses. However, if the atrial excitatory process during atrial fibrillation in horses is random as well, then an additional mechanism must be involved to produce the observed periodicity of the RR intervals. A clue may be found in the difference between the ventricular rates during atrial fibrillation in human beings and horses. This is ex-
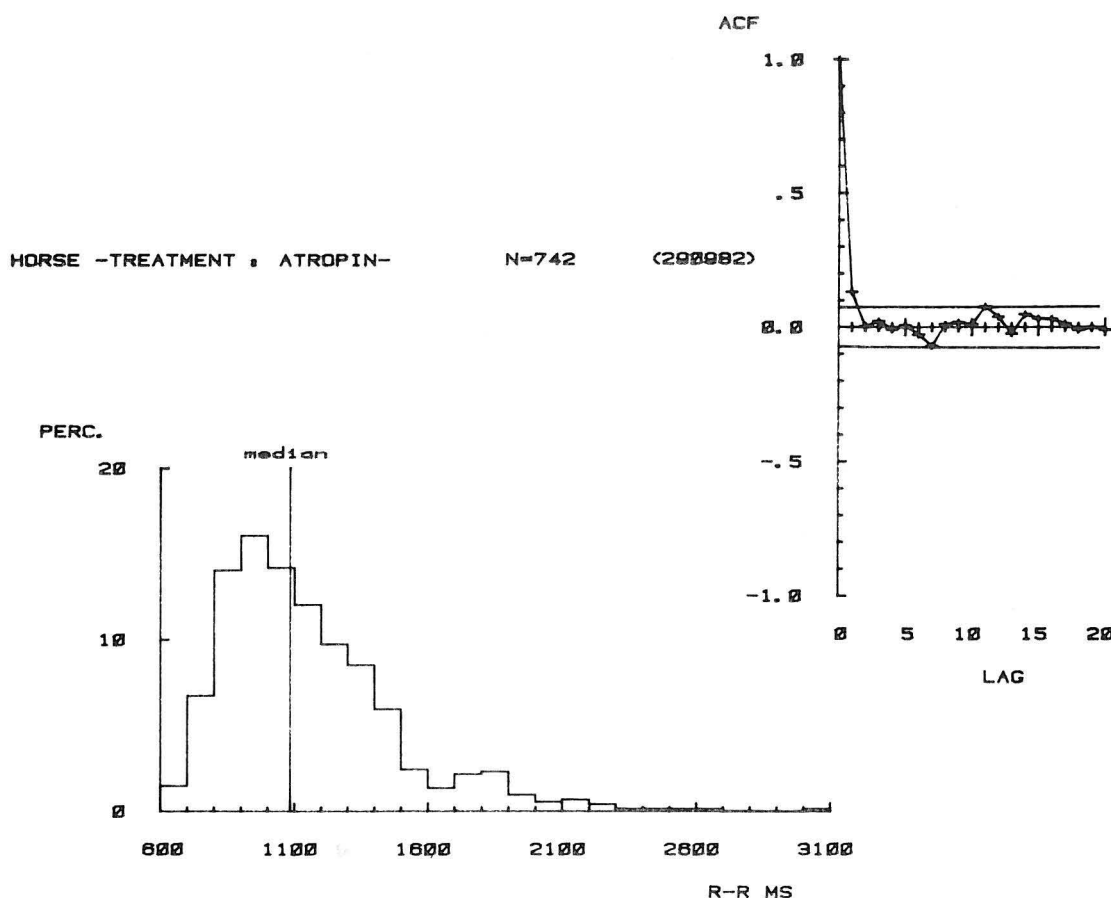
Figure 3. Histogram (**left**) and serial autocorrelogram (**right upper corner**) of Horse 4 (Table 1, episode 2) after digitalis treatment. Note the large number of very long intervals (4,450 ms) and the strong periodicity in the serial autocorrelograms. Abbreviations as in Figure 1.

emplified by the maximal duration of the RR intervals. In human beings these rarely exceed 2,000 ms, but in horses RR intervals of close to 4 or 5 seconds occur rather frequently. We reasoned that RR intervals of 3 seconds or more are sufficiently long to cause a considerable decrease in arterial blood pressure. This may trigger baroreceptor responses that could affect AV nodal conduction properties. We were able to substantiate this hypothesis by recording intraarterial pressure in one horse. During the long RR intervals, intraarterial pressure indeed decreased to less than 60 mm Hg (Fig. 5).

Borst et al. (24) could only induce prolongation of AV conduction time with electrical stimulation of the carotid sinus nerves in patients after a latency of 0.8 to 1.6 seconds. Therefore, RR intervals during atrial fibrillation in patients may just not be long enough to allow the baroreceptor response to interfere with AV conduction. Scher and Young (25) demonstrated that in unanesthetized dogs, sympathetic and vagal effects were combined when aortic pressure was lowered to 30 mm Hg below normal level. We never observed arterial pressure decreases of that magnitude during atrial fibrillation in patients or dogs. This offers another explanation why baroreceptor interference with AV conduction during atrial fibrillation in human patients may not

come into operation. In horses, the duration and degree of the blood pressure decrease suffice to induce reflex baroreceptor response, which may then affect AV conduction (26) and possibly also atrial muscle excitation. The large increase in RR interval after every fifth or sixth beat may thus result from an increase in vagal bursting as described by Ito and Scher (27).

Autonomic nervous system effects on AV conduction. Quinidine, which is known to have an atropine-like action (28), and atropine, which shortened RR intervals to slightly above 2,000 ms, abolished the periodicity in the serial autocorrelograms (Fig. 4) and reestablished the random pattern of ventricular rhythm. This makes it highly plausible that in horses the basic pattern of atrial excitation in atrial fibrillation is indeed random. Our hypothesis that nonrandom patterns of the ventricular rhythm in horses with atrial fibrillation is caused by autonomic nervous influences on AV conduction, secondary to long RR intervals, was
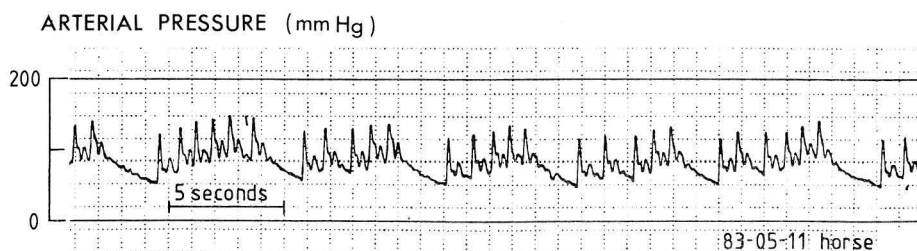
Figure 4. Histogram (**left**) and serial autocorrelogram (**right upper corner**) of Horse 7 (Table 1, episode 2) after atropine administration. The histogram is skewed and the serial autocorrelogram shows a pattern caused by a random sequence of the successive RR intervals. Abbreviations as in Figure 1.

further supported by the observation that digitalis, associated with more RR intervals of longer duration, induced an even stronger periodicity in the serial autocorrelogram (Fig. 3).

Role of respiratory-induced changes in autonomic discharge. The average respiratory rate of a horse corresponds reasonably well with the periodicity in the serial autocor-

relogram (Fig. 1). James et al. (29) demonstrated in dogs that bronchopulmonary-induced vagal reflexes can produce AV block during rapid sinus rhythms. Therefore, it cannot be excluded that respiratory-induced changes in autonomic discharge to the AV node are involved in the observed ventricular rhythm pattern.

Role of digitalis. One may ask why digitalis slows the ventricular rate during atrial fibrillation. It probably does so by two mechanisms. It 1) causes a lengthening of the shortest RR intervals by an increase in refractory period of the AV conduction system, and 2) produces more RR intervals of longer duration (2). What causes the digitalis-induced increase in number and duration of the long RR intervals during atrial fibrillation? Digitalis shortens the refractory

Figure 5. Intraarterial blood pressure recording of Horse 2. See text for details.

period of the atrial myocardium either directly or through vagal action (30), or both.

Shortening of the atrial refractory period during atrial fibrillation will result in more excitation waves that reach the AV junction within a certain time. More wave fronts at the AV junction will result in more concealed conduction and less impulses will proceed along the AV conduction tract (31). Consequently, more RR intervals of longer duration will be produced.

Cyclic shortening and lengthening of the atrial refractory period through a periodic change in vagal tone could cause a cyclic increase and a decrease in the number of wave fronts that reach the AV junction. Periodicity in the otherwise irregular ventricular rhythm would be the result. These cyclic variations in autonomic nervous discharge may also effect the electrophysiologic properties of the AV conduction system directly and, thus, cause or contribute to the enhanced periodicity in the serial autocorrelogram.

Duration of RR interval in horses versus human subjects. Finally, one might wonder why horses with atrial fibrillation have longer RR intervals than does the human patient with a similar arrhythmia. There is a direct relation between the duration of PR intervals and the size of the animal (32) and, thus, of the heart (33) and the AV node. The median RR interval during atrial fibrillation shows a similar relation with body size. Cardiac muscle is composed of individual cells that are rather uniform in diameter in all mammals (from the mouse to the whale) (34). The same is probably true for the average size of the AV nodal cells. Since the AV node of a horse is considerably larger than that of the human or canine AV node, it will contain significantly more cells. Assuming that there is a similar atrial excitation pattern in atrial fibrillation in horses, human beings and dogs, there will be a greater degree of concealed AV conduction because more AV nodal cells are available for concealment and, thus, longer RR intervals will occur.

Conclusion

Our former view (1–4) that the role of the AV junction in atrial fibrillation is limited to scaling down the number of atrial impulses by a subtle interplay between refractoriness and concealed conduction must be amended. Autonomic nervous activity may affect AV conduction and atrial refractoriness during atrial fibrillation in such a way that nonrandom ventricular rhythm patterns can occur. This does not happen in human beings because, in general, the RR intervals during atrial fibrillation are not long enough to induce autonomic nervous interferences. These observations further demonstrate that comparative pathophysiologic studies may contribute to better understanding of abnormal findings in human beings as already suggested by Lewis in 1912 (19). However, it is clear that this study in one of "the lower animals" has not settled the nature of the ventricular

irregularity during atrial fibrillation in human patients as we, like Lewis, had hoped.

References

1. Meijler FL, Strackee J, Van Capelle FJL, Du Perron JC. Computer analysis of the RR interval-contractility relationship during random stimulation of the isolated heart. Circ Res 1968;22:695–702.

2. Bootsma BK, Hoelen AJ, Strackee J, Meijler FL. Analysis of RR intervals in patients with atrial fibrillation at rest and during exercise. Circulation 1970;41:783–94.

3. Meijler FL. Atrial fibrillation: a new look at an old arrhythmia. J Am Coll Cardiol 1983;2:391–3.

4. Strackee J, Hoelen AJ, Zimmerman ANE, Meijler FL. Artificial atrial fibrillation in the dog; an artifact? Circ Res 1971;28:441–5.

5. Denes P, Wu D, Dhingra R, Pietras RJ, Rosen KM. The effect of cycle length on cardiac refractory periods in man. Circulation 1974;49:32–41.

6. Hoffman BF, Cranefield PF. The atrioventricular node. In: Electrophysiology of the Heart. New York: McGraw-Hill, 1960:132–74.

7. Langendorf R, Pick A, Katz LN. Ventricular response in atrial fibrillation: role of concealed conduction in the AV junction. Circulation 1965;32:69–75.

8. Moore EN. Observations on concealed conduction in atrial fibrillation. Circ Res 1967;21:201–8.

9. Knoebel SB, Fisch C. Concealed conduction. In: Brest AN, ed. Complex Electrocardiography 1. Cardiovascular Clin Philadelphia: FA Davis, 1973;5:21–34.

10. Billette J, Roberge FA, Nadea RA. Roles of the AV junction in determining the ventricular responses to atrial fibrillation. Can J Physiol Pharmacol 1975;53:575–85.

11. Heethaar RM, Robles de Medina EO, Meijler FL, et al. Response of AV nodal conduction to rate changes in rat, dog and man (abstr). Circulation 1981;64(suppl IV):IV–645.

12. Van Capelle FJL, Du Perron JC, Durrer D. Atrioventricular conduction in isolated rat heart. Am J Physiol 1971;221:284–90.

13. Billette J. Preceding His-atrial interval as a determinant of atrio-ventricular nodal conduction time in the human and rabbit heart. Am J Cardiol 1976;38:889–96.

14. Billette J. Short time constant for rate-dependent changes of atrioventricular conduction in dogs. Am J Physiol 1981;241:H26–33.

15. Harms FMA, Heethaar RM, Robles de Medina EO, Meijler FL. Atrioventricular nodal "memory" studied by random atrial stimulation (abstr). Am J Cardiol 1980;45:459.

16. Meijler FL, Heethaar RM, Harms FMA, et al. Comparative atrioventricular conduction and its consequences for atrial fibrillation in man. In: Kulbertus HE, Olsson SB, Schlepper M, eds. Atrial Fibrillation. Mölndal, Sweden: Astra Cardiovascular, 1982:72–80.

17. Deem DA, Fregin GF. Atrial fibrillation in horses: a review of 106 clinical cases, with consideration of prevalence, clinical signs, and prognosis. J Am Vet Med Assoc 1982;180:261–5.

18. Morris DD, Fregin GF. Atrial fibrillation in horses: factors associated with response to quinidine sulfate in 77 clinical cases. Cornell Vet 1982;72:339–49.

19. Lewis T. Irregularity of the heart's action in horses and its relationship to fibrillation of the auricles in experiment and to complete irregularity of the human heart. Heart 1911-1912;3:161–71.

20. Billette J, Nadeau RA, Roberge F. Relations between the minimum RR interval during atrial fibrillation and the functional refractory period of the AV junction. Cardiovasc Res 1974;8:347–51.

21. Scher AM, Heethaar RM, Zimmerman ANE, Meijler FL. Atrial rhythm during ventricular fibrillation in the dog. Circ Res 1976;38:41–5.

22. Rowland E, Curry P, Fox K, Krikler D. Relation between atrioventricular pathways and ventricular response during atrial fibrillation and flutter. Br Heart J 1981;45:83–7.

23. Heethaar RM, Denier van der Gon JJ, Meijler FL. Mathematical model of AV conduction in the rat heart. I. Cardiovasc Res 1973;7:105–14.

24. Borst C, Karemaker JM, Dunning AJ. Prolongation of atrioventricular conduction time by electrical stimulation of the carotid sinus nerves in man. Circulation 1982;65:432–4.

25. Scher AM, Young AC. Reflex control of heart rate in the unanesthetized dog. Am J Physiol 1970;218:780–9.

26. Schlepper M. Control of ventricular rate in atrial fibrillation: role of the autonomous nervous system. In Ref 16:307–18.

27. Ito CS, Scher AM. Reflexes from the aortic baroreceptor fibers in the cervical vagus of the cat and the dog. Circ Res 1974;34:51–60.

28. Goldman MJ. Quinidine treatment of auricular fibrillation. Am J Med Sci 1951;186:382–91.

29. James TN, Urthaler F, Hageman GR. Reflex heart block. Am J Cardiol 1980;45:1182–8.

30. Moe GK, Han J. Digitalis and the autonomic nervous system. In: Fisch C, Surawicz B, eds. Digitalis. New York, London: Grune & Stratton, 1969:110–7.

31. Mazgalev T, Dreifus LS, Bianchi J, Michelson EL. Atrioventricular nodal conduction during atrial fibrillation in rabbit heart. Am J Physiol 1982;243:H754–60.

32. Clark AJ. Conduction in the heart of mammals. In: Comparative Physiology of the Heart. Cambridge: Cambridge University Press, 1927:49–51.

33. Schmidt-Nielsen K. Circulation. In: Animal Physiology, Adaptation and Environment. 2nd ed. Cambridge: Cambridge University Press, 1979:99–100.

34. Sommer JR, Johnson EA. Comparative ultrastructure of cardiac cell membrane specializations. A review. Am J Cardiol 1970;25:184–94.