Comparative atrioventricular conduction and its consequences for atrial fibrillation in man

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Since the first description of atrial fibrillation by Hering [1] at the beginning of this century the irregular ventricular pattern has remained unexplained by clinicians and physiologists alike.

Not only does the underlying mechanism(s) of atrial fibrillation defy our full understanding, but the cause and nature of the irregular ventricular response have been and still are to a large extent "terra incognita" [2]. In his editorial in 1970 Brody [3] raised the question: ". . . what factors govern the response of the atrioventricular transmission system and the ventricles to the shower of impulses arriving from above?" For all practical and clinical purposes the ventricular response in patients with atrial fibrillation is considered to be random or, in other words, totally irregular. Lewis [4] left little doubt, when he stated that: "Amongst the distinguishing features [of auricular fibrillation] absolute irregularity of the ventricle is one of the most important." Again, Brody [3] called the question of the "absolute irregularity" perplexing. So it is, that nearly 80 years after Hering's [1] paper on the "Analyse des Pulsus irregularis perpetuus" the nature and degree of the ventricular irregularity in atrial fibrillation are still not fully understood.

Modern mathematical techniques including the use of digital computers have made it possible to analyse long recordings of the ventricular rhythm during atrial fibrillation. We have shown that in uncomplicated atrial fibrillation in man the ventricular rhythm is indeed absolutely irregular [5, 6]. Absolute irregularity in this context has been defined as a rhythm with random temporal sequences [3]. Intrinsic ventricular rhythmicity, found in dogs with atrial fibrillation, generated by rapid atrial stimulation does not occur during autochthonous atrial fibrillation [7].

The notion of a random ventricular rhythm during atrial fibrillation has been (and is) crucial, since from that finding we postulated that the refractory period of and concealed conduction in the atrioventricular (AV) nodal system failed to explain why the ventricular response is random. Moreover, neither digitalis

nor exercise changed the random character of the ventricular response, although the ventricular rate was affected by those interventions. We concluded: ". . . that the cause for the ventricular irregularity should be looked for somewhere else than in the AV system" [6].

These observations have aroused our interest regarding the role of the AV-conduction system in atrial arrhythmias in general, and atrial fibrillation in particular, and led us to study AV-nodal behaviour in patients and in animals by comparing well-defined pacing-induced atrial arrhythmias with their resulting AV-conduction times.

The objective of the study was to catch AV-nodal conduction in mathematical terms, so that predictions of PR or AH intervals during random (but well-defined) atrial rhythms could become possible. If this were to be successful, the resulting mathematical model could be used to measure the effect of drugs on AV-nodal conduction as well as to contribute to a better understanding of AV-nodal behaviour during atrial fibrillation in man.

Methods

Studies were performed over the years using 1) rat hearts both in situ and as isolated preparations, perfused according to the Langendorff technique [8, 9], 2) intact hearts of dogs (beagles) under general anaesthesia (N_2O/O_2 enflurance combination) and 3) patients undergoing electrophysiological investigations because of different types of atrial and/or ventricular arrhythmias.

The basic methodological approach was similar in rat, dog, and man. In each series, well-defined artificially induced atrial rhythms were initiated via bipolar stimulation at a site as close as possible to the sinus node. The stimulus strength was usually twice the threshold; stimulus duration was 2 milliseconds [10].

The induced rhythms consisted of:

1) stepwise changes in frequency from low to high rates, and vice versa,
2) extrasystoles after varying delays following each 8 or 10 basic intervals, and
3) random rhythms of different rates with either a uniform or a Gaussian distribution.

All random rhythms were produced (and analysed) by computer. An advanced 4-channel current source stimulator with comprehensive safeguards was developed for clinical use. Stimuli were applied in rats via direct stitched-on epicardial electrodes, in dog and man via bipolar stimulation catheters. The stimulation rates were so adjusted as to conform to the basic sinus rates of the hearts under study – high rates (2–8/second) being used in rats, and proportionately lower rates in dog and man. In patients the AV-nodal study protocol was performed after informed consent. Normal AV conduction was documented by incremental atrial pacing. None of the patients whose data were used for this particular study received cardioactive drugs at the time of the study. However, the results may have been affected by differences in age, sex, and underlying disease.

Patients were awake and unsedated implying that autonomic nervous influences might have been capable of influencing AV-nodal conduction. To assess this possibility, random atrial stimulation was applied in 5 patients before and after 1 mg atropine intravenously and 5 mg propranolol intravenously [11].

In the rat hearts PR intervals were measured using right atrial and left ventricular bipolar epicardial leads. In dog and man AV-nodal times were derived from His bundle electrograms, while Einthoven, lead II of the standard electrocardiogram, was recorded as well. In all instances changes in PR interval due to changes in atrial rhythm were caused by changes in AH intervals. The HV intervals always remained constant. In this fashion, we studied AV-nodal conduction in over 70 rat hearts, in 5 dogs and in 8 patients. Data are still being collected on dog and man. The intervals between stimulating pulses or the resulting PP or AA intervals were used as the input signals of the AV-nodal system in the animal studies. In a previous study [8] we demonstrated that stimulus-P intervals are constant at all stimulation intervals tested. In patients, only AA intervals have been used for our computations. The resulting PR or AH intervals were considered as the output signals of the system.

Results

Rats

A mathematical model of AV conduction in the rat heart was derived from PR intervals at several steady-state atrial stimulation rates and from the adaptation of stepwise changes in stimulating frequencies (Figure 1).

It appeared that the PR intervals after frequency steps either faster or slower could be described by a simple exponential relation (Figure 2).

From the parallel slopes of the semilogarithmic plots representing the relation between changes in PR intervals versus time elapsed after the frequency step, it could be concluded that AV-nodal conduction adaptation could be characterised for all steps by a single time constant.

This constant was in the same order of magnitude in all rat hearts studied. This

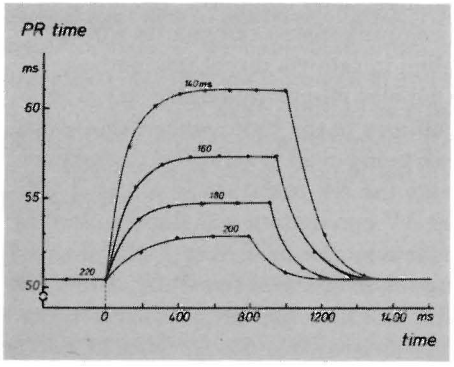

Figure 1. Plots of PR intervals after stepwise changes in stimulation intervals from 220 to 140, 160, 180, and 200 milliseconds and vice versa, versus the time after the step in the isolated rat heart.

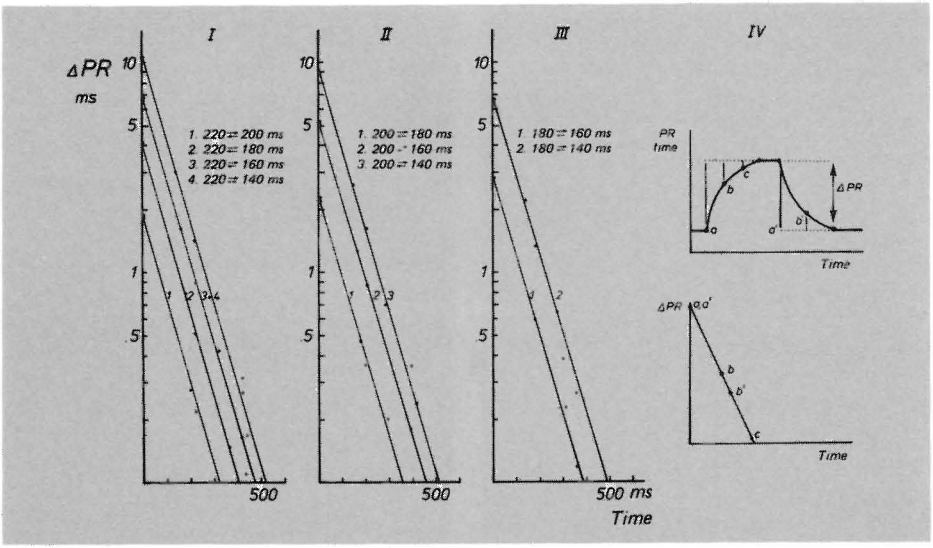

Figure 2. Semilogarithmic plots of changes in PR interval (see panel IV) versus the time elapsed after different steps in stimulation interval in the isolated rat heart.
Panel IV is a scheme of the exponential rise and decline of the PR time following stepwise changes in stimulation interval and the belonging semilogarithmic plot.

fairly simple mathematical relationship allowed us to "predict" PR intervals during random atrial stimulation for the isolated rat heart as well as for the rat heart in situ.

The detailed results of this study have been published in previous papers [8, 9].

Dogs

Adaptation of AV-nodal conduction was studied in the same fashion in intact beagles under general anaesthesia (see Methods). It appeared that AV-nodal conduction adaptation in the dog heart took fewer intervals to reach a new steady state than in rat hearts. AV-nodal conduction adaptation after an increase in frequency lasted longer than following a decrease in frequency. This difference (hysteresis?) between increasing and decreasing frequencies did not allow us to construct a mathematical model as simple as that in the rat.

Only adaptation of AV-nodal conduction following atrial extrasystoles after varying coupling intervals could be described by an exponential function (Figure 3).

The effect of random stimulation initiating beat-to-beat variations in AV conduction is demonstrated in serial cross-correlograms (Figure 4).

It can be seen that the first coefficient is strongly negative, the second coefficient is also negative but much weaker, while the third and higher order coefficients do not differ significantly from zero.

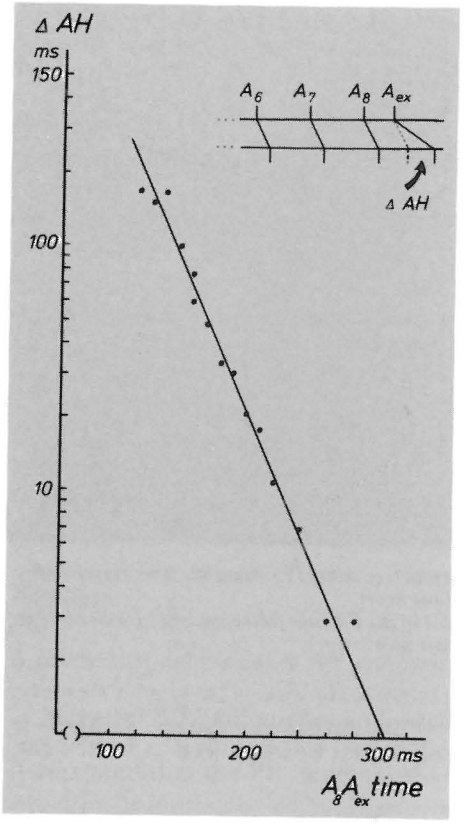

Figure 3. Semilogarithmic plot of changes in AH-conduction time versus varying coupling intervals of atrial extrasystoles. The atrial extrasystole is generated after each 8th basic interval.

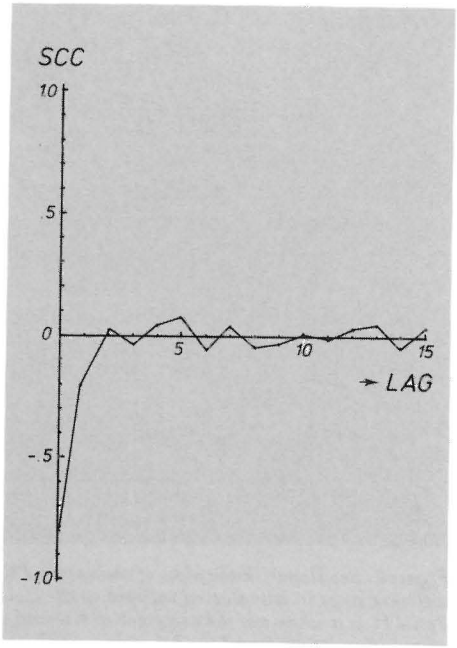

Figure 4. Serial cross-correlogram (SCC) of AH intervals versus AA intervals during random stimulation of the canine heart obtained from 200 successive intervals.

Patients

Figure 5 shows representative results obtained in one of our patients. It may be seen that adaptation of AV-nodal conduction to increases in frequency took only a few cardiac cycles to reach its new steady state.

As can be seen in Figure 5 a large frequency step (from a 800-millisecond AA interval to a 500-millisecond interval) takes more cardiac cycles for the AH time to adjust, than a small frequency step from 800 to 700 milliseconds. As in the dog, the time course of adaptation after an increase in frequency differs from the decrease in frequency. Adaptation after the downstep usually takes place within one cardiac cycle. The same phenomenon may be seen in the postextrasystolic AH time, which is always equal – within the error of measurement – to the pre-extrasystolic AH time, which also suggests a one-cycle adaptation of

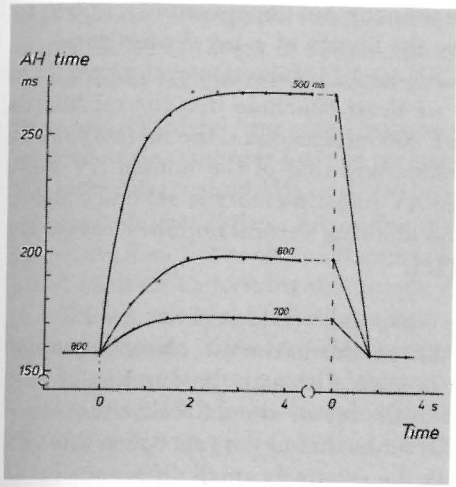

Figure 5. Plots of AH intervals after stepwise changes in atrial stimulation intervals from 800- to respectively 500-, 600-, and 700-millisecond intervals and vice versa versus the time after the step in the human heart.

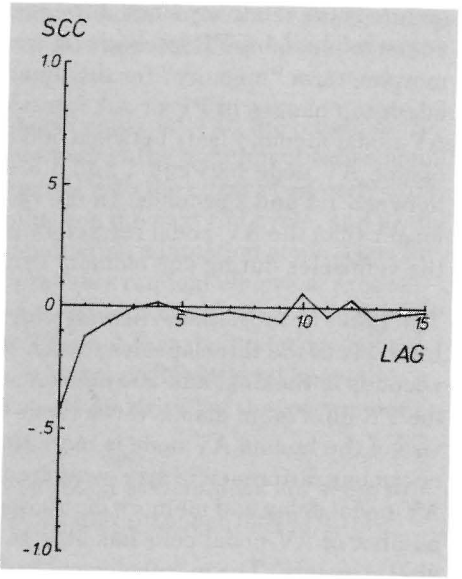

Figure 6. Serial cross-correlogram (SCC) of AH intervals versus AA intervals during random stimulation of the human heart obtained from 200 successive intervals.

the human AV node when going from a short to a long cycle. Human AV-nodal adaptation also shows an exponential pattern following induced atrial extrasystoles after varying delays. The exponential increase in AV-conduction time after atrial extrasystoles with decreasing delays may also be observed after the first AA interval of each step with an increasing frequency (Figure 5). Cross-correlograms were computed between atrial intervals and AH-conduction times from records obtained during random atrial stimulation (interval range 350–700 milliseconds) (Figure 6).

The first coefficient showed a negative correlation (in the order of –0.5) between directly preceding atrial intervals and AH-conduction times. Second and higher order coefficients did not differ significantly from zero.

In spite of observed changes in AV-nodal refractoriness similar results were obtained after autonomic nervous blockade [11].

Discussion

It took us 10 years from when we observed the existence of a random ventricular rhythm in patients with atrial fibrillation in 1970 to develop a quantitative description of the function of the intact human AV node.

Taking an overall view of the results in rat, dog, and man the most remarkable

feature is the relatively small difference in time the AV-nodal system requires to adjust to changing PP intervals. If we take the liberty of using the anthropomorphic term "memory" for the time the AV-nodal conduction system needs to adapt to changes in PP or AA intervals, we must conclude that the rat heart's AV-nodal memory lasts between 500 and 1 000 milliseconds, the memory of the canine AV node between 1 and 1.5 seconds, and that of the human AV node between 1.5 and 2 seconds. In the rat, the AV-nodal memory is several times longer than the AV-nodal refractory period allowing several impulses to reach the ventricles during one memory cycle [12].

The ratios of these times fit well with the comparable values of normal PR intervals in the three species; about 70 milliseconds in the rat, about 140 milliseconds in the dog, and 200 milliseconds in man. Although the duration of the PR interval in man is three times that in the rat we should realise that the size of the human AV node is more than 50 times that of the rat. Given this enormous difference in size compared with the relatively small difference in AV-nodal delay and memory in rat, dog, and man we may conclude that the total number of AV-nodal cells has little to do with the delay and adaptation of this vital structure. The morphological and/or anatomical structure of the human AV node has been studied in detail [13]. The site of AV-nodal delay seems well established [14]. The morphological substrate of the adaptation feature of the AV-conduction system is not yet known. We may speculate that it may be only a small group of cells within the total structure of the AV node. This fits well with a theoretical analysis of AV conduction using an analogue model of the AV node [15]. The analogous time ratios between AV-nodal delay and AV-nodal memory in the three species may suggest that the same group of cells that are responsible for AV-nodal delay [14], may be the site of AV-nodal memory.

We have found that in the dog and in the human heart the adaptation of the AV-conduction system to stepwise increases in frequency differs from the stepwise decrease in frequency. This finding must have its consequences for AV-nodal behaviour during atrial fibrillation, because there is a continuous variation of short and long cycles.

The demonstrated characteristics of human AV-nodal adaptation to frequency steps, atrial extrasystoles (exponential pattern) and random stimulation (one cycle "memory") may give us more insight into the chemicophysical properties of the AV-nodal system and its role as a relay-station between atria and ventricles.

The relatively short memory of the human AV node in relation to the average RR interval of the ventricular rhythm in atrial fibrillation must contribute to maintenance of the random pattern of the ventricular rhythm. We do not know whether the memory cycle of the human AV node is triggered by a conducted impulse (the H spike on the His bundle electrogram) or by the shower of blocked and/or partially penetrating impulses from the atria. There is good reason to assume

that only the propagated impulses set off the AV-nodal memory, because during atrial fibrillation most of the atrial impulses that approach the AV node proper are blocked high in the AV-nodal structure [16].

Because AV-nodal "memory" in man is short compared with the length of the cardiac cycles, there is little or no potential to affect the duration of subsequent RR intervals. A short HH cycle (to be compared with the effect of an early atrial extrasystole) has little or no tendency to influence the next HH cycle, and a long HH cycle does not seem to influence AV-conduction adaptation at all. Thus the atrial excitations forming the unique and probably random electrical process [17] known as atrial fibrillation return scaled down, but still random in the RR interval pattern of the ventricular rhythm. The fact that the "memory" of the human AV node is not much longer than the average RR interval is another factor in explaining the "perplexing absolute irregularity" of the ventricular rhythm in the presence of atrial fibrillation.

Thus we have two reasons why the AV-conduction system does not seem to contribute to the random pattern of the ventricular response during atrial fibrillation:

- the aforementioned short memory of the AV node in relation to the average RR interval during atrial fibrillation
- earlier evidence [6] that interventions that decrease or increase the ventricular rate during atrial fibrillation do not affect the random character of the ventricular rhythm

The combination of these two arguments supports the view that ventricular irregularity during atrial fibrillation is caused by the random excitatory process of the atria itself. The role of the AV node is confined to scaling down the number of atrial impulses and this is accomplished by a subtle interplay between refractoriness and concealed conduction [18].

Conclusions

1. The differences in AV-nodal conduction time and in AV-nodal memory, the latter defined as the time AV-nodal conduction takes to adjust to changes in PP or AA interval between rat, dog, and man are small compared with the difference in size of the AV node.
2. Although the location within the AV-nodal structure responsible for the AV-nodal memory is not known, it seems fair to assume that it can be confined to only a relatively small number of cells (N region?).
3. The ratios between AV-nodal delay (AH interval) and AV-nodal memory of rat, dog, and man are more or less similar. This could favour the assumption that it is the same group of cells.
4. Human AV-nodal memory is relatively short compared with average RR intervals in atrial fibrillation. This phenomenon may contribute to the fact that the ventricular rhythm in patients with atrial fibrillation shows a random pattern.

Acknowledgments

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