Atrioventricular Nodal Response to Retrograde Activation in Atrial Fibrillation

FRED H.M. WITTKAMPF,* M.Sc., MIKE J.L. DE JONGSTE,** M.D., and
FRITS L. MEIJLER,*** M.D.

From the *Heart-Lung Institute, Section of Cardiology, University Hospital of Utrecht, **Department of Cardiology, Thoraxcenter, University Hospital of Groningen, and ***The Interuniversity Cardiology Institute of the Netherlands

Atrioventricular Nodal Reset. Retrograde (ventriculoatrial) conduction that reaches the atrioventricular node simultaneous with, or just before an atrial impulse can facilitate subsequent anterograde conduction. However, a spontaneous or programmed ventricular extrasystole during atrial fibrillation is generally followed by a compensatory pause indicating subsequent delayed anterograde transmission. This characteristic response was used as a model to study the mechanism of atrioventricular nodal behavior during atrial fibrillation. In eight medically-treated patients with chronic atrial fibrillation and a relatively slow but random ventricular response, single premature right ventricular stimuli were delivered after every eighth spontaneous R wave during at least 1 hour. A fixed coupling interval of the extrastimulus, considerably shorter than the shortest spontaneous RR interval, was used. The histograms of the postextrasystolic intervals were compared with those of the spontaneous noninterrupted RR intervals. The average postextrasystolic interval was 180 to 300 msec longer than the mean control RR interval, and in six of eight patients, the shape of the histogram of the postextrasystolic cycles was insignificantly different from that of the spontaneous RR intervals. This suggests that in those six patients, the retrograde impulse had reset the random timing cycle of atrioventricular nodal discharge during atrial fibrillation. This observation is compatible with the hypothesis that electrotonically-mediated propagation across a weakly coupled junctional area within the atrioventricular node, rather than decremental conduction and extinction of anterograde atrial impulses at different levels within the node, may be the mechanism of atrioventricular transmission in atrial fibrillation. (*J Cardiovasc Electrophysiol*, Vol. 1, pp. 437-447, October 1990)

atrial fibrillation, concealed conduction

Introduction

The rate and irregularity of the ventricular rhythm in atrial fibrillation (AF) is generally thought to result from decremental conduction and extinction of anterograde fibrillatory impulses at different levels within the atrioventricular (AV) node (Langendorf, 1948; Moe, et al., 1964; Langendorf, et al., 1965; Moore, 1967; Moore,

et al., 1971; Mazgalev, et al., 1982; Dreifus and Mazgalev, 1988). However, the effect of spontaneous and elicited ventricular extrasystoles in patients with AF have raised doubts about this classical interpretation (Langendorf, 1948; Langendorf and Pick, 1971; Neuss, et al., 1984; Morady, et al., 1986; Wittkamp, et al., 1988; Meijler and Fisch, 1989).

In a previous paper, we demonstrated that during AF, right ventricular pacing at pacing intervals that were considerably longer than the shortest spontaneous RR intervals, all anterograde conduction was abolished and the RR interval sequence became regularized to the pacing interval (Wittkamp, et al., 1988). On the basis of this finding, we questioned the validity of the classical theory of concealed conduction to

This study was supported by the Wijnand M. Pon Foundation, Leusden, The Netherlands.

Address for correspondence: Fred H.M. Wittkamp, M.Sc., Heart-Lung Institute, Section of Cardiology, University Hospital Utrecht, 100 Heidelberglaan, 3584 CX, Utrecht, The Netherlands.

Manuscript received 13 April 1990; Accepted for publication 2 July 1990.

explain rate and irregularity of the ventricular rhythm in AF. Instead, we and others offered the hypothesis that the AV junction may act as an automatic focus, its pacemaker function being electronically modulated by disorganized atrial fibrillatory waves (Cohen, et al., 1983; Wittkamp, et al., 1988; Meijler and Fisch, 1989).

This hypothesis can be investigated by a more detailed analysis of the effect of single retrograde AV nodal activations on subsequent anterograde conduction. However, retrograde AV nodal penetration and analysis of the so-called compensatory pause following ventricular extrasystoles is hindered by the unpredictability of anterograde AV nodal activation and by the random character of the ventricular response during AF (Brody, 1970; Bootsma, et al., 1970; Watt, et al., 1984). A sufficiently large number of compensatory pauses following properly timed ventricular extrasystoles must therefore be analyzed to reveal their characteristic properties (Bootsma, et al., 1970; Watt, et al., 1984).

The purpose of our study was, first, to investigate the mechanism of the compensatory pause following retrograde AV nodal penetration in AF and second, at the same time, using the phenomenon to clarify the role of the AV node in the generation of the randomly irregular ventricular rhythm in AF.

Methods

Retrograde conduction of early premature ventricular stimuli may be blocked by refractoriness of the His-Purkinje system (Akhtar, et al., 1975). When the ventricular extrasystole is

elicited relatively late, that is, shortly before the next expected anterogradely conducted ventricular complex, it may collide with an otherwise successfully conducted anterograde impulse within the His-Purkinje system. Only with an intermediate coupling interval, the retrograde impulse will be able to reach the AV node. Therefore, in patients with AF, single premature ventricular stimuli were delivered more than approximately 200 msec before the earliest next expected spontaneous R wave and more than 400 msec after the onset of the preceding QRS complex. Thus, only patients with spontaneous RR intervals not shorter than 600 msec were selected for this study. To avoid patient discomfort and risk during this kind of study, we decided to investigate only patients with an already implanted multiprogrammable ventricular pacemaker.

Indications for pacemaker implantation had been either symptomatic sick sinus syndrome or AF with dizzy spells or syncope, or both (Table 1). The patients with sick sinus syndrome developed permanent AF after pacemaker implantation. All patients had some form of medical treatment that was maintained through the study.

Right ventricular extrastimuli were delivered by programming the pacemaker to the synchronous mode and by triggering the pacemaker with external stimuli via electrodes on the thorax. With a lowest programmable pacing rate of 30 ppm, and an expected compensatory pause following premature ventricular stimulation, the longest spontaneous RR interval should not exceed 1,800 msec to allow measurement of all spontaneous ventricular intervals.

TABLE 1
Relevant Clinical Data of the Eight Patients

Patient Number	Age Year and Sex	Symptoms*	Antiarrhythmic Agents	Associated Conditions
1	68M	Syncope	Disopyramide	MVR
2	81M	DS	Alprenolol	SSS*
3	65F	DS	Digitalis	-
4	62M	DS	Metoprolol Digitalis	SSS*, MVR
5	55M	DS	Mexiletine Metoprolol Digitalis	-
6	67M	DS	Disopyramide Digitalis	SSS*
7	79F	DS, Syncope	Disopyramide Digitalis	-
8	74M	DS	Digitalis	SSS*

AF = atrial fibrillation; DS = dizzy spells; F = female; M = male; MVR = mitral valve replacement; SSS = sick sinus syndrome. *Symptoms before pacemaker implantation

Patient Selection

The criteria for patient selection were as follows:

Sustained AF with a random ventricular response;

An implanted ventricular pacemaker that could be programmed to the synchronous mode and a basic rate of 30 ppm;

A spontaneous RR interval distribution between approximately 600 and 1,800 msec.

Stimulation Protocol

The basic rate of the implanted pacemaker was programmed to 30 ppm and its pacing mode to synchronous (triggered). At least 100 spontaneous R waves were recorded on an electrocardiographic inkjet recorder to obtain the duration of the shortest RR interval. A programmable external stimulator was connected to two surface electrodes on the thorax and its sensitivity was adjusted to ensure reliable detection of the QRS synchronized impulses from the implanted pacemaker. Next, the external stimulator was programmed to deliver one extrastimulus after each eighth detected QRS-synchronized implanted pacemaker artifact.

The strength of the external stimulus was adjusted to ensure reliable detection by the implanted pacemaker so that it would trigger the delivery of the extrastimuli to the right ventricle. The coupling interval of the extrastimulus was set at least 200 msec shorter than the shortest spontaneous RR interval, but outside the effective ventricular refractory period. This situation was maintained for 60 to 90 minutes. During this period, the electrocardiogram was continuously recorded on f.m. magnetic tape (R-71, TEAC Corporation of America, Montebello, CA).

The following protocol was used:

- (1) Programming of the implanted pacemaker to the synchronous mode and a basic rate of 30 ppm, and 15-minute rest;
- (2) Ten-minute recording until approximately 500 consecutive spontaneous RR intervals were obtained;
- (3) Sixty- to 90-minute recording with delivery of single extrastimuli with a fixed coupling interval after each eighth R wave.

Analysis of the Electrocardiogram

The synchronized pacing spikes of the implanted pacemaker simplified analysis of spontaneous RR and postextrasystolic (SR)

intervals using a specially-made detector circuit. All intervals were rounded to 10 msec and stored in digital format on a desk computer (HP 85, Hewlett Packard, Andover, MA) and digital data cassettes. RR intervals before and after spontaneous ectopic premature ventricular complexes and episodes with muscle potential interference were deleted from analysis. A histogram and an autocorrelogram of the first 10-minute episode without pacemaker interference were made to verify the randomness of the spontaneous ventricular rhythm. The coupling interval of the extrastimulus (RS) was defined as the delay between QRS onset and the extrastimulus, and SR as the interval between extrastimulus and the onset of the next spontaneous QRS complex. Thereafter, the RR and SR intervals were measured and the histograms of those intervals calculated for each patient.

After informed consent, eight patients with chronic AF and a low spontaneous ventricular rate volunteered to be included in the study. The histogram and autocorrelogram of these patients confirmed the randomness of their ventricular rhythm. Patients 1 and 3 volunteered for a second investigation during which the extrastimulus was applied after a longer delay.

Statistical Analysis

To compare the shape of the two histograms, they had to be shifted relative to each other. As shift, we took the difference between the mean values of RR and SR intervals, rounded to 10 msec (Table 2). The class width (W) used for quantification of the two histograms was related to the spread (S) in SR interval and the number of SR intervals (N) according: $W = \sqrt{(S/N)}$ (rounded to 10 msec). The spread was defined as the difference between the outer 2.5% limits of the histogram of SR intervals. Kolmogorov-Smirnov analysis (Zar, 1974) was then performed in an approach to reject the supposition that the two histograms were different (Appendix 1). A P value of 0.05 was used as the level of statistical significance.

Results

The electrocardiogram of patient 3 is shown in Figure 1. In this patient, the delay between QRS onset and the ineffective synchronous impulse from the implanted pacemaker was 50 msec, whereas the delay between external trigger and the extrastimulus was 10 msec. The coupling interval of the extrastimulus delivered by the external stimulator was set at 400 msec, and thus

TABLE 2

Comparison of Spontaneous RR Interval and Postextrasystolic Interval Distribution in the Eight Patients

Patient Number	RR msec	Mean RR msec	RS msec	SR msec	Mean SR msec	Shift msec	Histogram Shape Difference
1	930-1530	1186	660	1230-1780	1485	300	NS
2	870-1660	1362	680	1060-1830	1554	190	NS
3	730-1560	1050	460	1030-1870	1353	300	NS
4	760-1980	1276	550	1020-2000	1569	330	S
5	720-1460	1030	430	870-1790	1287	260	NS
6	670-1490	1030	460	900-1700	1239	210	NS
7	920-2000	1346	640	1140-2000	1529	180	NS
8	670-1240	928	450	900-1430	1185	260	S
1*	970-1630	1251	1050	1040-1810	1407	160	S
3*	720-1630	1053	560	930-1800	1309	260	NS

All timings except main intervals are rounded to 10 msec; *Second investigation. RS = Coupling interval of the extrastimulus; SR = Interval between extrastimulus until the onset of the next spontaneous R wave; NS = not significant; S = significant.

the extrastimuli from the implanted pacemaker were delivered $400 + 50 + 10 = 460$ msec after the onset of the preceding QRS complex. In seven out of eight patients right and left skewed, as well as rather symmetrical histograms were obtained. In one patient (number 4), the histogram of spontaneous RR intervals was bimodal with two peaks at both ends of the spectrum. The

histogram of the spontaneous RR intervals and that of the postextrasystolic SR intervals of patient 1 are shown in Figures 2A and 2B, respectively. Apart from a relative shift of 300 msec, the shape of the two histograms looks similar. Kolmogorov-Smirnov analysis of the two histograms revealed that the difference in shape was not statistically significant. The results of the

Figure 1. ECG of patient 3 with atrial fibrillation during the period in which single extrastimuli were delivered. The middle part of this tracing is enlarged in the lower half of this figure. The coupling interval of the trigger impulse from the external stimulator relative to preceding QRS synchronized impulse from the implanted pacemaker is 400 msec. The coupling interval between QRS onset and the right ventricular extrastimulus (RS) is 460 msec.

HISTOGRAM OF RR INTERVALS

Figure 2A. Histogram of spontaneous RR intervals during the first investigation in patient 1 (Table 2). The spontaneous RR intervals are measured during the period in which single extrastimuli were delivered after each eighth spontaneous R wave.

HISTOGRAM OF SR INTERVALS

Figure 2B. Histogram of SR intervals in patient 1. The shape of the histogram is not different from that of the histogram of spontaneous RR intervals as shown in Figure 2A. The shift between these two histograms is approximately 300 msec. RS = coupling interval between the onset of a spontaneous R wave and the extrastimulus delivered by the implanted pacemaker; SR = interval between extrastimulus from the implanted pacemaker until the onset of the next spontaneous R wave.

investigation in all patients are summarized in Table 2. The extrasystolic coupling interval (RS) varied from 430 to 680 msec, and was 190 to 290 msec shorter than the shortest spontaneous RR interval. In patients 4 and 7, the maximal SR interval was truncated to 2,000 msec due to the escape interval of the implanted pacemaker. In these cases, the medians of both histograms were used to shift their relative position before

comparison. In six out of eight patients, the same results were obtained: the shape of the histogram of the postextrasystolic cycles did not differ significantly from that of the spontaneous RR intervals; and the relative shift between both was 180 to 300 msec (mean 240 msec).

In patients 4 and 8, the shape of the two histograms was significantly different (Table 2). In both patients, one of the two histograms was bimodal; a second peak was the main reason for the difference in histogram shape. The two histograms of patient 8 are shown in Figures 3A and 3B

HISTOGRAM OF RR INTERVALS

Figure 3. Histogram of spontaneous RR intervals of patient 8.

HISTOGRAM OF SR INTERVALS

Figure 3B. Histogram of SR intervals in patient 8. In this patient the shape of this histogram is different from that of the spontaneous RR intervals as shown in Figure 3A. The shape is bimodal and suggests the presence of a second mechanism of AV transmission or a subsidiary junctional pacemaker. RS = coupling interval between the onset of a spontaneous R wave and the extrastimulus; SR = interval between extrastimulus until the onset of the next spontaneous R wave.

Figure 4A. Histogram of spontaneous RR intervals during the second investigation in patient 1.

In patients 1 and 3, the study was repeated with a different extrasystolic delay. In patient 1, with the shortest RR of 970 msec, the extrastimulus was delivered 1,050 msec after the onset of the preceding R wave, so some of the extrastimuli came too late to activate the ventricles. These cycles were excluded before analysis. In contrast to the finding at the shorter coupling interval of 660 msec, the shape of the histogram of SR intervals in this patient now differed significantly from that of the spontaneous RR intervals (Figs. 4A and 4B, Table 2). In the second investigation in patient 3, the extrasystolic coupling interval was increased from 460 to 560 msec, which was still relatively short. In this patient, with both coupling intervals, the shape of the histogram of SR and RR intervals remained identical. As a check for the sensitivity of Kolmogorov-Smirnov analysis, the histograms of RR and SR intervals of each patient were compared with the corresponding histograms of the other seven patients. The outcome of this analysis was that the shape of all histograms of RR as well as SR intervals was significantly different from those of the other patients.

Discussion

The finding that the shape of the histogram of SR intervals is similar to that of the spontaneous RR intervals strongly suggests that a retrograde ventricular impulse can reset the timing cycle of AV nodal activation during AF. This observation challenges the classical concept that graded properties of the AV node cause decremental conduction and extinction of atrial impulses at different levels within the node (Langendorf,

Figure 4B. Histogram of SR intervals during the second investigation in patient 1. The extrastimulus from the implanted pacemaker is delivered relatively late in the cardiac cycle at 1,050 msec. The shape of the histogram is significantly different from that of the spontaneous RR intervals in Figure 4A. RS = coupling interval of the extrastimulus; SR = interval between extrastimulus until the onset of the next spontaneous R wave.

1948; Moe, et al., 1964; Langendorf, et al., 1965; Moore, 1967; Moore, et al., 1971; Mazgalev, et al., 1982; Dreifus and Mazgalev, 1988) and provides supportive evidence for the hypothesis that during AF the AV node behaves as the pacemaker for the ventricles (Wittkamp, et al., 1988; Meijler and Fisch, 1989).

The Compensatory Pause in Atrial Fibrillation

Pritchett et al. (1980) have studied the characteristics of the so-called compensatory pause in patients with AF by scanning the cardiac cycle with single ventricular extrastimuli. The coupling interval was held constant for five premature ventricular complexes. Their study confirmed the presence of a compensatory pause, but a relation between the compensatory cycle and the extrasystolic coupling interval or the spontaneous RR interval was not found. However, Watt et al. (1984) demonstrated that estimates of average ventricular rate in supine patients with chronic AF has to be based on at least 30 seconds of electrocardiographic data or approximately 50 cycles. Thus, to study the effect of timing of a premature ventricular excitation on the mean duration of the compensatory pause, at least 50 extrastimuli are required. For the analysis of more detailed characteristics of the compensatory pause, even more intervals are needed.

Scaling of the Atrial Rhythm

Kirsh et al. (1988) analyzed the irregularity of the high right atrial electrogram and of the ventricular response during atrial fibrillation in patients with and without an accessory AV connection. No significant difference was found between the variation coefficients of the atrial and ventricular rhythms in patients of either group. From this, they concluded that scaling down of the irregular atrial rhythm could account for the ventricular response in AF, regardless of the nature of the AV conduction pathway. Indeed, if each ventricular interval would be a multiple of one atrial interval, the mean RR interval, as well as its SD, would be multiplied with the same scaling factor. However, this cannot be the case. Scaling of the fibrillatory potentials with a factor N implies that each N th event is followed by one R wave. When these fibrillatory atrial potentials are randomly timed, the SD of the sum of N cycles does not increase with a factor N , but with the square root of N (Armitage and Berry, 1987). With a constant scaling factor, the finding of Kirsh et al. (1988) would imply that the properties of the AV node as well as of the accessory AV connection contribute significantly to the irregularity of the ventricular rhythm. With a varying scaling factor, the irregularity of the RR intervals can reach any value, and conclusions about a relationship between the atrial and ventricular rhythm in individual patients cannot be drawn from correlations between both variation coefficients.

Interception of Anterograde Impulses

With the same reasoning, a lengthening of the interval between two anterograde impulses (for example by a ventricular extrasystole) will have its effect on the variability of their interval. We checked this by measuring the histogram of the duration of two consecutive spontaneous RR cycles. The shape of those "double RR interval" histograms differed significantly from the histogram of single RR intervals and from that of the SR intervals in all patients. As expected, the standard deviation of the irregularity of these "double RR intervals" is approximately $\sqrt{2}$ times that of the single RR intervals. Interception of an anterograde impulse by a ventricular extrasystole with a fixed coupling interval would therefore broaden the histogram of compensatory pauses. As this is not the case, our results cannot satisfactorily be explained on the basis of interception of one R wave by the ventricular extrasystole.

Lengthening of AV Nodal Refractoriness

The classical explanation of the compensatory pause is that concealed retrograde invasion lengthens AV nodal refractory period (Langendorf, 1948; Moe, et al., 1964; Langendorf, et al., 1965; Moore, 1967; Dreifus and Mazgalev, 1988). This lengthening then would have to be equal to the sum of the RS interval and the relative shift of the histogram of SR intervals. This would imply a lengthening of the refractory period of the AV node of approximately 800 msec (Table 2) by one single retrograde penetration. Moreover, this lengthening of AV nodal refractoriness would have to be constant for each elicited premature ventricular complex to explain the similarity between the two histogram shapes. However, with the varying RR intervals in AF, a constant effect on AV nodal refractoriness by retrograde penetration is unlikely. As discussed above, lengthening of the interval between anterograde impulses alone would also change the shape of the histogram of compensatory pauses.

Modification of Subsequent Anterograde Conduction

Lehmann et al. (1984) showed that during sinus rhythm, an interpolated concealed retrograde impulse can increase AV nodal delay of the next anterograde impulse. This has been used to explain the compensatory pause in atrial fibrillation. However, the much longer interval between the two consecutive anterogradely conducted R waves (RS + SR) would cause a much broader histogram of SR intervals, as explained before. Moore and others (Moore, et al., 1971; Moore and Spear, 1971; Shenasa, et al., 1983) also demonstrated facilitation of anterograde conduction of otherwise blocked or delayed anterograde impulses by preceding concealed retrograde conduction. This is explained by peeling back of distal AV nodal refractoriness by earlier retrograde activation. According to the classical concept of decremental anterograde conduction in AF, a substantial number of atrial impulses normally delayed and blocked within the AV node would become suitable candidates for facilitated conduction following concealed retrograde penetration. Our study does not show any facilitation of anterograde conduction that suggests that conduction of single well-organized atrial activations through the AV node might differ from that of erratic fibrillatory atrial impulses.

Concealed Conduction in Atrial Fibrillation

This study, as well as our previous study, demonstrates that the electrophysiological explanation for concealed conduction, as offered by Langendorf and later experimentally confirmed does not seem to be applicable in patients with AF and seemingly normal AV behavior (Langendorf, 1948; Moe, et al., 1964; Langendorf, et al., 1965; Moore, 1967; Moore, et al., 1971; Mazgalev, et al., 1982; Dreifus and Mazgalev, 1988). While random ventricular rhythm in AF should be contributed to the random input by the fibrillating atria, the scaling down of the atrial rate does not seem to be caused by decremental conduction and extinction of atrial impulses at different levels within the AV node. Our previous and current findings could never be explained if the AV node were to behave as a filter. In other words, the concealed conduction theory does neither stand the test of programmed and spontaneous ventricular extrasystoles nor the effect of continuous right ventricular pacing during AF. Therefore, other mechanisms residing in the AV node have to cause ventricular rate and rhythm during AF.

The Atrioventricular Nodal Pacemaker Hypothesis

Our results can be explained on the basis that during AF, the AV node behaves as an unprotected pacemaker that is reset by retrograde activation. The observed shift of the histogram of SR intervals relative to the histogram of spontaneous RR intervals will then correspond with the sum of the stimulus latency, the retrograde conduction time of the premature ventricular complex, and the anterograde conduction time of the following spontaneous R wave.

Several investigators have studied the behavior of the AV node with mathematical or electronic modeling (Grant, 1956; Katholi, et al., 1977; Cohen, et al., 1983; West, et al., 1985; van der Tweel, et al., 1986). The general outcome of these studies is that the electrophysiological properties of the AV node can indeed be explained on the basis of an entrained biological oscillator. Our study in patients with AF suggests that this hypothesis may also apply in AF. This raises the dilemma that the AV node or a part of it behaves as the element that determines the ventricular rhythm whereas manifest pacemaker activity, i.e., spontaneous phase 4 depolarization has never been observed within the node during AF (Moore, 1967; Mazgalev, et al., 1982).

Unifying Explanation

Apart from manifest pacemaker activity within the AV node, another mechanism may explain our results. Rosenbleuth (1958) has suggested a "step delay" at a localized region of the AV node. Billette (1987) studied AV nodal conduction during premature atrial stimulation in isolated rabbit heart preparations and found a silent time zone between N and NH cell activation. He suggested the existence of an inactivation or stagnation gap within the node with electrotonic impulse transmission across the gap. Recently McKinnie et al. (1989) investigated the influence of blocked beats on conducted beats in a model of 2:1 AV block. They also suggested electrotonic transmission across a step delay within the AV node. Cranefield et al. investigated electrotonic interaction between weakly coupled excitable cells (Cranefield, et al., 1971; Jalife, 1983; Antzelevitch and Moe, 1983). Nonconducted impulses originating from a proximal segment were found to delay or advance the approach to threshold of a subsequent impulse (Jalife, 1983; Antzelevitch, et al., 1983). This can lead to an irregular and chaotic-like response in rhythmically driven nonoscillatory cardiac conducting tissues (Chialvo and Jalife, 1987). Moreover, distal excitability can also be reset by direct stimulation of the distal site (Antzelevitch and Moe, 1983). Jalife (1983) already demonstrated the striking similarities between the behavioral characteristics of the sucrose gap model and those of an intact AV node. Our investigation also contributes to these studies by suggesting that the transmission of irregularly spaced and inefficient fibrillatory impulses through the AV node can be explained on the basis of electrotonic influence. The distal side of a weakly coupled junctional area can thus behave as the "rhythm determining element" or pacemaker of the ventricle without the need for manifest pacemaker activity within the node. This can explain the random ventricular rhythm and the compensatory pause in AF as well as the resetting phenomenon described in this study (Cranefield, et al., 1971; Jalife, 1983; Antzelevitch and Moe, 1983; Chialvo and Jalife, 1987).

Limitations of the Study

We cannot readily explain the findings in patients 4 and 8, in which the shape of the histogram of SR intervals differed significantly from that of the spontaneous RR intervals. These

were the only patients in which one of the two histograms showed a second peak. In both patients, the autocorrelogram indicated a random ventricular rhythm. However, the extra peak in the histogram of spontaneous RR intervals in patient 4 and in the histogram of SR intervals in patient 8 (Fig. 3B) suggests that other mechanisms, such as dual AV nodal pathways or a subsidiary pacemaker, might have played a role in the generation of these ventricular events (Kirsh, et al., 1988).

It would have been preferable to study patients without cardioactive medications. However, due to their rather high ventricular rate, these patients usually do not fulfill the criteria of the study protocol. The possibility that the patients of this study may have had some sort of AV nodal abnormality or drug effect cannot be excluded. However, all patients had a randomly irregular spontaneous ventricular rhythm, which has been considered as evidence of normal AV nodal conduction during AF (Bootsma, et al., 1970).

One might furthermore question whether the protocol used in this study is the most effective to investigate AV nodal function during AF. For instance, one can expect an effect of the extrasystolic coupling interval on the histogram of SR intervals as long as the extrastimulus reaches the AV node. A parallel shift of the postextrasystolic R wave in concert with the extrasystolic delay would be further proof of AV nodal resetting. However, such an investigation for obtaining histograms of SR intervals at different RS intervals would require several hours of recording. Second, in most patients, the interval available for extrasystolic stimulation with a varying delay is limited.

Akhtar et al. (1975) demonstrated that the effective refractory period of ventricular myocardium was shorter than the retrograde effective refractory of the His-Purkinje system in 17 of 23 patients. Therefore, an effective extrastimulus outside of the ventricular refractory period does not necessarily imply retrograde AV nodal penetration. Consequently, the RS interval had to be somewhat longer than the ventricular effective refractory period, but at the same time at least 200 msec earlier than the estimated earliest spontaneous R wave.

During long-term ECG recording, a slow trend in ventricular rate may alter the RR as well as the SR intervals. Since both intervals are almost certainly affected in the same fashion, these variations in rate will not affect the outcome of

the comparison of corresponding histograms and thus of the study.

Conclusions

In six of eight patients with chronic AF, the mean "compensatory pause" after single relatively early premature ventricular stimuli was 180 to 300 msec longer than the mean spontaneous RR interval, whereas the shape of both histograms was not significantly different. The apparent ability to reset a random discharge cycle in the AV node during AF, suggests that the distal side of a weakly coupled junctional area inside the AV node behaves as a pacemaker for the ventricular rhythm during AF. The results of this study challenge the classical concept that graded properties of the AV node cause decremental conduction and elimination of anterograde impulses at different levels within the node and are incompatible with the hypothesis that the AV node behaves as a passive filter that scales down randomly-spaced fibrillatory atrial impulses.

Acknowledgments: We express our gratitude for the encouragement and constructive comments of Jose Jalife, M.D., Syracuse, Michiel J. Janse, M.D., Amsterdam, and Etienne O. Robles de Medina, M.D., Utrecht. We thank Jan Res, M.D., Amsterdam, Wim L. Mosterd, M.D., and Henk van Rooyen, Amersfoort, who selected the patients, and Ingeborg van der Tweel, Utrecht, who assisted with the statistical analysis. Part of the equipment was kindly supplied by Vitatron Medical BV, Dieren, The Netherlands.

Appendix 1

Statistical Analysis

The "Kolmogorov-Smirnov goodness of fit" test has been used to compare an observed with a reference distribution (Zar, 1974). In our application, the spontaneous RR interval distribution serves as the reference to investigate the SR distribution. Because the total number of measured intervals is different for both histograms, the number of RR intervals has to be normalized before comparison. This is done by multiplication of the number of RR intervals in each class (n_R) with the ratio between the total number of SR and of RR intervals. Comparison between both histograms is then performed by calculation of the maximal difference between the corresponding cumulative sums of successive histogram classes as shown in the example below.

The maximal absolute difference (D) between cumulative n'_R and cumulative n is divided by the number of SR intervals and compared with the theoretical Kolmogorov-Smirnov values, which

APPENDIX TABLE 1

Class #	RR Histogram n_R	Expected Histogram $n'_R = n_R * 145/268$	SR Histogram n_S	Cum. n'_R	Cum. n	D
1	1	0.5	0	0.5	0	5.0
2	12	6.5	5	7.0	5	2.0
3	49	26.6	27	33.6	32	1.6
4	106	57.3	49	90.9	81	9.9
5	65	35.2	37	126.1	118	8.1
6	24	13.0	18	139.1	136	3.1
7	11	5.9	9	145.0	145	0
8	0	0	0	145.0	145	0
Total	$N_R = 268$		$N_S = 145$			

depend on the level of statistical significance. With a P value of 0.05, the critical value of D for 145 events is 0.11, whereas $9.9/145 = 0.068$. Hence, the two populations in this example are not significantly different when a P value of 0.05 is used as the level of statistical significance.

References

- Akhtar M, Damato A, Batsford WP, Ruskin JN, et al: A comparative analysis of antegrade and retrograde conduction patterns in man. *Circulation* 1975;52:766-779.
- Antzelevitch C, Moe G: Electrotonic inhibition and summation of impulse conduction in mammalian Purkinje fibers. *Am J Physiol (Heart Circ Physiol)* 1983;245:H42-H53.
- Armitage P, Berry G: *Statistical Methods in Medical Research*. Second Edition. Blackwell Scientific Publications, Oxford, 1987;p.90.
- Billette J: Atrioventricular nodal activation during premature stimulation of the atrium. *Am J Physiol (Heart Circ Physiol)* 1987;252:163-177.
- Bootsma BK, Hoelen AJ, Strackee J, Meijler FL: Analysis of R-R intervals in patients with atrial fibrillation at rest and during exercise. *Circulation* 1970;41:783-794.
- Brody DA: Ventricular rate patterns in atrial fibrillation. *Circulation* 1970;41:733-735.
- Chialvo DR, Jalife J: Non-linear dynamics of cardiac excitation and impulse propagation. *Nature* 1987;330:749-752.
- Cohen RJ, Berger RD, Dushane TE: A quantitative model for the ventricular response during atrial fibrillation. *IEEE Trans Biomed Eng* 1983;30:769-780.
- Cranefield PF, Klein HO, Hoffman BF: Conduction of the cardiac impulse. *Circ Res* 1971;28:199-219.
- Dreifus LS, Mazgalev T: "Atrial paralysis": Does it explain the irregular ventricular rate during atrial fibrillation? *J Am Coll Cardiol* 1988;11:546-547.
- Grant RP: The mechanism of A-V arrhythmias. *Am J Med* 1956;20:334-344.
- Jalife J: The sucrose gap preparation as a model of AV nodal transmission: Are dual pathways necessary for reciprocation and AV nodal "echoes"? *PACE* 1983;6:1106-1122.
- Katholi CR, Urthaler F, Macy J Jr, James TN: A mathematical model of automaticity in the sinus node and AV junction based on weakly coupled relaxation oscillators. *Comp Biomed Res* 1977;10:529-543.
- Kirsh JA, Sahakian AV, Baerman JM, Swiryn S: Ventricular response to atrial fibrillation: Role of atrioventricular conduction pathways. *J Am Coll Cardiol* 1988;12:1265-1272.
- Langendorf R: Concealed AV conduction: The effect of blocked impulses on the formation and conduction of subsequent impulses. *Am Heart J* 1948;35:542-552.
- Langendorf R, Pick A, Katz LN: Ventricular response in atrial fibrillation: Role of concealed conduction in the AV node. *Circulation* 1965;32:69-75.
- Langendorf R, Pick A: Artificial pacing of the human heart. *Am J Cardiol* 1971;28:516-525.
- Lehmann MH, Mahmud R, Denker S, Soni J, et al: Retrograde concealed conduction in the atrioventricular node: Differential manifestations related to level of intranodal penetration. *Circulation* 1984;70:392-401.
- McKinnie J, Avitall B, Caceres J, Jazayeri M, et al: Electrophysiologic spectrum of concealed intranodal conduction during atrial rate acceleration in a model of 2:1 atrioventricular block. *Circulation* 1989;80:43-50.
- Mazgalev T, Dreifus LS, Bianchi J, Michelson EL: Atrioventricular nodal conduction during atrial fibrillation in rabbit heart. *Am J Physiol* 1982;243:H754-H760.
- Meijler FL, Fisch C: Does the atrioventricular node conduct? *Br Heart J* 1989;61:309-315.
- Moe GK, Abildskov JA, Mendez C: An experimental study of concealed conduction. *Am Heart J* 1964;67:338-356.
- Moore EN: Observations on concealed conduction in atrial fibrillation. *Circ Res* 1967;21:201-208.
- Moore EN, Knoebel SB, Spear JF: Concealed conduction. *Am J Cardiol* 1971;28:406-413.
- Moore EN, Spear JF: Experimental studies on the facilitation of AV conduction by ectopic beats in dogs and rabbits. *Circ Res* 1971;29:29-39.
- Morady F, Dicarlo LA, Ryszard JR, Krol B, et al: An analysis of post-pacing R-R intervals during atrial fibrillation. *PACE* 1986;9:411-416.
- Neuss H, Golling FR, Schlepper M, Thormann J, et al: Regularisierung der Kammerintervalle bei Vorhofflimmern-elektrophysiologische Befunde zum zugrundeliegenden Mechanismus. *Z Kardiol* 1984;73:106-112.
- Pritchett ECL, Smith WM, Klein SJ, Hammill SC, et al: The "compensatory pause" of atrial fibrillation. *Circulation* 1980;62:1021-1025.
- Rosenbluth A: Functional refractory period of cardiac tissues. *Am J Physiol* 1958;194:171-183.

Shenasa M, Denker S, Mahmud R, Lehmann MH, et al: Atrioventricular nodal conduction and refractoriness after intranodal collision from antegrade and retrograde impulses. *Circulation* 1983;67:651-660.

van der Tweel I, Herbschleb JN, Borg C, Meijler FL: Deterministic model of the canine atrio-ventricular node as a periodically perturbed, biological oscillator. *J Appl Cardiol* 1986;1:157-173.

Watt JH, Donner AP, McKinney CM, Klein GJ: Atrial fibrillation: Minimal sampling interval to estimate average rate. *J Electrocardiol* 1984;17:153-156

West BJ, Goldberger AJ, Rovner G, Bhargava V: Non-linear dynamics of the heartbeat. *Physica* 1985;17D:198-206.

Wittkampff FHM, de Jongste MJL, Lie KI, Meijler FL: Effect of right ventricular pacing on ventricular rhythm during atrial fibrillation. *J Am Coll Cardiol* 1988; 11:539-545.

Zar JH. The Kolmogorov-Smirnov goodness of fit. In: McElroy WD, Swanson CP, eds. *Biostatistical Analysis*. Prentice-Hall, Inc., Englewood Cliffs, N.J., 1974;p.54 .