Atrial arrhythmias and measurement of the wavelength in a chronic dog model

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Atrial arrhythmias and measurement of the wavelength in a chronic dog model

Atrial arrhythmias and measurement of the wavelength in a chronic dog model

Academisch Proefschrift

ter verkrijging van de graad van Doctor in de Geneeskunde
aan de Rijksuniversiteit Limburg te Maastricht,
op gezag van de Rector Magnificus, Prof. Dr. F.I.M. Bonke,
volgens het besluit van het College van Dekanen,
in het openbaar te verdedigen
op vrijdag 23 januari 1987 om 16.00 uur.

door

Pieter Lodewijk Rensma

geboren te Rotterdam

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Aan mijn Vader

Voor Ans

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CHAPTER I

INTRODUCTION

Disturbances of cardiac rhythm have been described since Harvey in 1628 gave the first account of a fibrillating heart (Harvey 1628). However, like the origin of the normal heart beat, its source remained "...as mysterious as the source of the Nile" (Abercromby 1685) and it took more than two centuries before further explorations were made to reveal the nature of several cardiac rhythms. At the end of the 19th century, a surge of studies on the mechanical activity of the heart during abnormal rhythms led to an already detailed description of the rhythm and amplitude of contraction during atrial flutter and atrial and ventricular fibrillation. Further progress came within reach with the development of instruments which visualized phenomena not perceptible to the naked eye. The introduction of the string-galvanometer by Einthoven (1901, 1903) made it possible to record the electrical impulse which directs the mechanical events in the heart. By studying the sequence of electrical activation of the heart, concepts regarding the mechanism of cardiac arrhythmias could be investigated. By then, basically two different mechanisms underlying cardiac arrhythmias had been proposed: 1. abnormal impulse formation and 2. abnormal impulse conduction leading to circuitous propagation and reentry. In the following years evidence has accumulated that the second mechanism forms the basis of the far majority of atrial tachy-arrhythmias. Therefore, we shall continue to discuss the concept of reentrant excitation in the heart.

Circus movement around an anatomical obstacle.

The first hints to the concept of circus movement of excitation as a cause of cardiac arrhythmias were presented by McWilliam in his paper on fibrillar contraction of the heart (1887). However, these were mere specu-

lations and it was not until 1906 before the first direct observations of circulating excitation were made by Mayer. In his classic experiment, he created a loop of contractile tissue by cutting the centre out of the discoid body of a jellyfish. By applying a stimulus to the preparation he was able to initiate a circulating contraction wave in the ring. From these studies he already inferred some basic characteristics of circus movement as was shown by his statement that "the circuit must be long enough to allow each point to rest for an appreciable interval of time before the return of the wave" (Mayer 1908). However he did not show much notion of the importance of his observations for cardiology. One who did understand the relevance of his studies for clinical arrhythmias was Mines. In a ring preparation made from atrial and ventricular tissue of the tortoise heart, he could start a contraction wave passing from ventricle to atrium, back to the ventricle and so on (Mines 1913). He immediately suggested that circulating excitation may be responsible for some cases of clinical paroxysmal tachycardia. Furthermore, he formulated a number of conditions which are of paramount importance for the initiation of circulating excitation: the occurrence of unidirectional block, which permits the impulse to travel in only one direction, and slow conduction of the impulse so as to allow the tissue ahead of the impulse to restore its excitability, which is further promoted by a short refractory period. These conditions allow the block area to recover its excitability before the impulse approaches it from the opposite direction and the impulse can reenter its point of origin.

These features of circus movement, which today are considered indispensable for reentry to occur, were already acknowledged on the basis of naked eye and kymographic registration of the movements of the contraction wave in preparations of jellyfish and of tortoise heart. It was Lewis who showed the validity of the circus movement hypothesis in atrial tachy-arrhythmias in the in situ dog's heart (Lewis et al. 1920). By way of mapping the sequence of electrical activation, he demonstrated that experimentally induced atrial flutter was based on circus movement of the impulse around the orifices of the superior and inferior caval vein. The studies on circulating excitation around central anatomical obstacles in the heart were extended by Rosenblueth and Garcia Ramos (1947). By crushing the atrial tissue between the orifices of the caval veins, they increased the size of the continuous block area, which resulted in an easier initiation and longer

continuation of atrial flutter. Manipulation of the size of the anatomical obstacle established the relationship between circuit length, conduction velocity and flutter rate, a lengthening of the pathway or a slowing of the conduction of the impulse causing an increase in revolution time. With the knowledge on circus movement increasing, the concept was more widely accepted and investigators started to use the Rosenblueth/Garcia Ramos model of atrial flutter also for the study of possible modes of action of pharmacological agents in human flutter (Brown 1952). For a review of the early studies on circus movement and atrial flutter see Rydand (1966).

The first evidence that circus movement in an anatomically determined circuit can form the basis for tachycardias in humans was provided by Durrer and coworkers (1967a, 1967b) in their studies on patients suffering from the Wolff-Parkinson-White syndrome. As already suggested by Mines (1913, 1914), the existence of an accessory bundle between atrium and ventricles, as present in these patients, provides a circuitous pathway for the excitation wave involving the atria, the normal AV connection, the ventricles and back to the atria via the accessory bundle. By means of epicardial mapping and programmed electrical stimulation of the heart, Durrer et al. (1967a, 1967b) showed that entrapment of the impulse in this route can indeed cause reciprocal tachycardias in man. In the following decade, Wellens et al. greatly extended the knowledge on mechanism and treatment of tachycardia in different manifestations of the syndrome (for reviews see Wellens 1975, Wellens et al. 1980 and 1984). By applying the principles of circus movement laid down by Mines (1913, 1914), they unraveled the significance of differences in electrophysiological properties of the various components of the circuit and their pharmacological manipulation for the initiation and termination of tachycardia. Mines' ultimate test of circulating excitation (i.e. cutting the circuit should stop the arrhythmia) is therapeutically applied in this syndrome: pharmacological blockade of conduction or surgical interruption of the pathway, usually effected at the accessory bundle, frees the patient from life-threatening arrhythmias. Until now this pathway forms the only unambiguously demonstrated anatomical reentrant circuit in the human heart.

Circus movement without an anatomical obstacle: functional, intramyocardial reentry.

The above examples of reentry are all based on circus movement around a central anatomical obstacle. However, Garrey in 1914 had already introduced the idea that "...natural rings are not essential for maintenance of circus contractions." Sixty years later Allesie et al. (1973) gave experimental proof for this proposition. In a piece of isolated rabbit atrium, they were able to induce circus movement which was determined by the electrophysiological properties of the myocardium and not by a pre-existent anatomical pathway. In this type of reentrant circuit no excitable gap exists between the crest and the refractory tail of the excitation wave and the circuit will assume the smallest possible size allowed by the present electrophysiological properties. Therefore, the perimeter of the circuit is equal to the length of the excitation wave (refractory period x conduction velocity). The centre of the circuit is held continuously refractory by the circulating impulse. By a shortening of the refractory period the central area becomes earlier excitable and the impulse can follow a shorter route. On the other hand, an increase of the conduction velocity results in a larger circuit size, because the impulse, arriving earlier, has to circumvent areas which have not had sufficient time to recover excitability. However there still exists a tight fit between the head and the tail of the excitation wave, and thus the revolution time of the impulse is solely determined by the length of the refractory period.

In atrial fibrillation, functional reentry is considered to play a major role. During this arrhythmia, multiple wavefronts are simultaneously wandering through the atrium. In a computer model of atrial fibrillation, Moe and coworkers showed that during a rapid rhythm local differences in refractoriness can cause the impulse to degenerate in multiple daughter wavelets, which continuously invade areas which have just recovered excitability (Moe et al. 1959). In this way chaotically moving wavefronts and reentrant circuits are set up, completely determined by the functional properties of the tissue. Persistence of fibrillation is dependent on the average number of wavelets simultaneously present in the tissue mass. The lower their number, the higher the chance of their synchronous inactivation and thus of the termination of the chaotic rhythm. This theory was experi-

mentally validated by mapping the activation pattern in canine atria during fibrillation (Allessie et al. 1985).

Thus a number of striking differences between anatomically and functionally determined reentry exists. First, in "anatomical" reentry site and length of the pathway are fixed, whereas in case of a functional circuit localization of the pathway and size of the circuit are variable. Secondly, in "anatomical" reentry the length of the circuit is equal to the length of the anatomical pathway, whereas the length of a functional circuit is determined by the length of the excitation wave. Thirdly, in "anatomical" reentry there exists a gap of full excitability, which is absent in functional reentry. Such an excitable gap makes it possible to reset or even terminate the circus movement with extraneous impulses, whereas the excitation pattern in functional circuits will not be interfered with by oncoming wavefronts. Fourthly, the revolution time of an anatomical circuit is determined by the conduction velocity of the impulse and the length of the pathway. In "functional" reentry, the revolution time is equal to the refractory period in the circuit. Thus drugs which depress conduction will slow only the rate of "anatomical" reentry. On the other hand, changes in refractoriness will proportionally affect the rate of "functional" reentry, but it will leave the revolution time of an anatomically determined circuit unchanged. A concise representation of the differences in properties between purely anatomically or functionally determined reentrant circuits is given in figure 1.1.

By mapping the sequence of electrical activation in experimental models it was shown that the two types of circus movement described above can cause atrial tachy-arrhythmias. Atria in which inexcitable scars have been produced classically form the substrate of atrial flutter based on "anatomical" reentry (Rosenblueth et al. 1947, Brown 1952, Kimura et al. 1954, Hayden et al. 1967). Atrial flutter in intact healthy canine atria was shown to be based on functional reentrant circuits (Allessie et al. 1984). The question arises which of the two types of circus movement is active in human reentrant tachycardias. For obvious reasons total mapping of the excitation pattern is usually not possible. However, taking in mind the different properties of the two types of reentry, also without complete

CIRCUS MOVEMENT

Anatomically determined
(Mines, 1913)

1. Fixed length and localization of circuit.
2. Circuit length equal to anatomical pathway.
3. Excitable gap between head and tail of impulse.
4. Rate proportional to conduction velocity and length of pathway.

Functionally determined
(Allessie et al. 1977)

1. Variable size and localization of circuit.
2. Circuit length equal to the length of the excitation wave.
3. No gap of full excitability.
4. Rate proportional to refractory period.

Figure 1.1: Comparison of characteristics of anatomically and functionally determined circus movement.

mapping of the circuit inferences about the present type of circus movement can be made. Electrical stimulation of the heart has proved to be a powerful technique to study the mechanism of human tachycardias (Wellens 1978). In a series of patients with atrial flutter, Wellens (1971) showed that pacing of the high right atrium did not influence time relations of the tachycardia. However, when stimulation was carried out low in the right atrium, flutter could be reset by premature atrial stimulation and terminated by overdrive pacing. These results pointed to the existence of either a small reentrant circuit or an unprotected focus low in the right atrium. Also for the study of ventricular arrhythmias, programmed stimulation proved a very effective method. The ability to initiate and terminate ventricular tachycardias in the post-infarction period by well-timed extra-stimuli strongly suggested the existence of a reentrant circuit with an excitable gap (Wellens et al. 1972, 1974). The widespread application of programmed electrical stimulation in the following years resulted in the recognition of two types of atrial flutter (Wells et al. 1979). These authors divided 27 cases of atrial flutter in a slower type I (with a cycle length of 175-250 ms) which could be influenced by rapid atrial pacing, and a faster type II flutter (cycle length 140-175 ms) which did not respond to atrial pacing. The rather slow rate of the type I flutter, its conversion by rapid pacing and the reset of the flutter cycle by a properly timed single stimulus all point to the existence of some type of anatomically determined reentry circuit with an excitable gap (Waldo et al. 1977, Watson et al. 1980, Inoue et al. 1981, Disertori et al. 1983, Klein et al. 1986). On the other hand, the failure of overdrive pacing to convert rapid atrial flutter (type II) indicates that the excitable gap is either very small or absent. Therefore, rapid atrial flutter might be based on functionally determined reentry.

Apart from programmed electrical stimulation, also the response of the flutter rate to drugs may give clues as to which form of reentry is present. In dogs with atrial enlargement due to tricuspid insufficiency, compounds known to shorten atrial refractoriness increased the flutter rate, whereas drugs which prolong atrial recovery time slowed the rate of the flutter (Boyden 1986). Similar observations were made in atrial flutter in dogs with sterile pericarditis (Okumura et al. 1984). These results were taken as evidence that the flutter was based on functional, intramyocardial reentry.

Circus movement with a partly excitable gap.

It should be emphasized however that the two forms of circus movement described above represent the extremes of a continuum, and it has been proposed that a third form of circus movement, in which aspects of the other two types are present in varying degrees, is active in the pathogenesis of human tachycardias (Allessie et al. 1984, Wellens et al. 1984, Boineau 1985). The response to programmed stimulation or pharmacological agents can vary in this form of mixed reentry and will depend on the size and properties of the existing excitable gap. The recent observations by Frame et al. (1986) in a model of atrial flutter support this view. In dogs with circus movement around the tricuspid ring, there appeared to be incomplete recovery of excitability even by the end of the excitable gap which existed in the circuit. Therefore, despite the presence of an excitable gap, shortening of atrial refractoriness by vagomimetic agents increased the flutter rate. The central anatomical obstacle determines a fixed location of the circuit and tends to stabilize circus movement because short-circuiting of the impulse is prevented by the obstacle. On the other hand, the response to pharmacological agents is determined by the size and the degree of recovery of the excitable gap. With a large and completely recovered excitable gap, the circuit will exhibit all characteristics of anatomically determined reentry. However, the smaller the excitable gap and the less recovery of its excitability, the more the circuit will behave like a functionally determined type of circus movement. In diseased myocardium the setup of circuits with a mixture of both functional and anatomical characteristics is likely. The localization of such circuits will be fixed and the resulting tachycardia can be expected to be long-lasting. Success in reset or termination of the tachycardia by programmed stimulation will depend on the pacing site.

Factors determining the initiation and persistence of reentrant arrhythmias.

- Inhomogeneity in electrophysiological properties
- Length of the excitation wave
- Tissue mass

Inhomogeneity in refractoriness and conduction velocity.

The occurrence of unidirectional and temporal conduction block is a prerequisite for the initiation of reentry because it forces the impulse in a circuitous route around the non-excitable area, after which the impulse may retrogradely reenter its point of origin. During a normal slow rhythm such block areas will not be present in the healthy heart because all fibers have had sufficient time to recover excitability, and an extra-systole originating late in the cardiac cycle will spread radially over the myocardium. However a premature impulse arising in the relative refractory period will only propagate in fibers which are already excitable, whereas it will block in areas which are still refractory. Thus the presence of adjacent areas with different refractory periods was shown to cause unidirectional block of a premature impulse and consequently the initiation of intra-atrial reentry (Alessie et al. 1976, Boineau et al. 1980). Great disparity in excitability in closely adjacent ventricular fibers is probably also of crucial importance for the setup of reentrant circuits following abnormal impulse formation in the acute phase of myocardial infarction, leading to ventricular tachycardias and fibrillation (Downar et al. 1977, Janse et al. 1980, 1981). In the normal atrium, dispersion of refractoriness is naturally present and is reported to be affected by heart rate and autonomic tone. Han et al. (1966) showed that the temporal dispersion of recovery of excitability in the canine atrium diminished at increasing heart rates, whereas artificial vagal stimulation is known to increase dispersion of atrial refractoriness (Alessi et al. 1958, Ninomiya 1966, Zipes et al. 1974). In the clinical situation, an increased asynchrony of recovery of excitability has been associated with the vulnerability to paroxysmal atrial fibrillation (Michelucci et al. 1982).

Apart from dispersion in duration of refractoriness, also spatial differences in conduction properties dependent on myocardial architecture may lead to non-uniform conduction. In a microscopic preparation of a canine atrial muscle bundle, Spach et al. (1981) observed preferential conduction in the longitudinal direction of the fibers during slow pacing. However, early premature impulses propagated decrementally and finally extinguished longitudinally, whereas slow but stable propagation was evident in the transverse direction of the fibers. Clearly, also the anisotropic proper-

ties of myocardium may cause local conduction block, thereby favouring the occurrence of reentry. However, the occurrence of unidirectional block is not the only prerequisite for the creation of a reentrant circuit. It is the length of the excitation wave which determines whether the impulse can reenter or not, when retrogradely approaching the area of conduction block.

The length of the excitation wave and reentry.

For the initiation and continuation of reentry in the ring-like structures of Mayer (1906) and Mines (1913) two conditions must be present: there should be a temporal conduction block, transverse through the ring, on one side of the stimulus site, and the point of origin of the impulse must be excitable again when the wave arrives from the opposite side. The latter prerequisite is fulfilled when the length of the excitation wave (which is the distance travelled during the refractory period) is shorter than the pathway around the obstacle, leaving part of the circuit fully excitable (Lewis 1925).

In functional reentrant circuits, no gap of full excitability exists and the size of the circuit is therefore equal to the length of the excitation wave. The size of the unidirectional block needed for the initiation of this type of circus movement, is proportional to the wavelength of the impulse. With a small area of block and a long wavelength, retrograde reentry of the area where antegrade conduction failed is prevented by insufficient recovery of excitability. If however the wavelength is short in relation to the length of the area of block, the impulse can complete the reentrant loop and proceed for subsequent circus movements. The natural occurring inhomogeneity in the atrial myocardium may cause small functional blocks. When the wavelength is short, these small areas of conduction block may suffice to set up reentry circuits. On the other hand, when the wavelength is long, a large area of conduction block is required to make the impulse reenter. Because in the normal atrial myocardium the occurrence of large areas of conduction block is unlikely, a long wavelength will prevent the initiation of reentrant tachycardias.

It should be noted that for the initiation of circus movement around an anatomical obstacle in the intact atria, also a functional block area

measuring at least half the perimeter of the obstacle is required in order to prevent collision of two impulses circumventing the obstacle in opposite directions. Only when the obstacle is very near to another inexcitable area (simulating the situation in the models of Mayer and Mines), a small area of conduction block bridging these two structures may be sufficient to allow reentry.

The wavelength is also important in the perpetuation of reentrant rhythms. Interventions which prolong the wavelength will increase the size of intramyocardial reentrant circuits. This may be expected to result in interruption of the circuit when it outgrows the available tissue mass. If an excitable gap is present, prolongation of the wavelength will first reduce and finally close the excitable gap, leading to instability of the circuit and a high chance of block of the circulating impulse. When multiple wandering wavelets are present, as during atrial fibrillation, an increase in circuit size will diminish the possible number of wavelets and thus increase the likelihood of termination of the arrhythmia. On the other hand, interventions which shorten the wavelength will enhance the perpetuation of reentrant circuits and may even lead to degeneration of one circuit in multiple wavefronts.

Considering these concepts of reentry, determination of the length of the excitation wave seems an useful tool in assessing the chances of its occurrence. It can be done by direct mapping of the pathway of intramyocardial reentrant circuits (Allessie et al. 1977, 1984), but this is a very elaborate method and unfeasible in intact animal models. A more convenient method for measurement of the wavelength was recently developed by Smeets et al. (1983, 1986). Its principles are depicted in figure 1.2. The upper panel gives a schematical representation of a functional reentrant circuit. The black area is in its inexcitable phase, the dotted area represents relative refractory tissue. The head of the activation wave (arrow) bites in the refractory tail of the circulating impulse. Because no excitable gap exists, the size of the circuit is equal to the length of the excitation wave. The lower panel shows how the wavelength can be measured in a strip of myocardium. The circle is unfolded, and now the wavelength is equal to the length of the straight pathway covered by the impulse in the time needed for recovery of excitability. This distance is given by the product of the conduction velocity of the impulse and the refractory period. Smeets

Figure 1.2: Schematic drawing of a functionally determined reentrant circuit. The black area represents tissue which is in its inexcitable phase, whereas the dotted area indicates relatively refractory tissue. Because there exists no excitable gap between head and tail of the excitation wave, the size of the circuit is determined by the wavelength of the impulse. By unfolding the circle the wavelength can be represented in a straight pathway. The length of this pathway (WL) is given by the product of refractory period (RP) and conduction velocity (CV).

et al. (1986) showed that the wavelength measured in this way in strips of rabbit atrium equaled the size of intramyocardial circuits in segments of atrial myocardium during different circumstances. Thus, measurement of conduction velocity and refractory period in bundles of atrial myocardium is a reliable method for determination of the perimeter of functional reentrant circuits.

Tissue mass and fibrillation.

The relationship between heart size and the stability of fibrillation was already described by McWilliam (1887), who observed an increased tendency to recover from this arrhythmia in smaller animal species. By cutting fibrillating ventricles to increasingly smaller pieces, Garrey (1914)

determined the minimal mass required for sustained fibrillation. He could cease fibrillation in the tips of the auricles by isolating them functionally with a clamp, while the remaining major mass of the atria continued to fibrillate. Subsequent studies have extended the evidence that atrial mass is of major importance in the occurrence of atrial fibrillation (Boswell et al. 1968, Bohn et al. 1971, Moore et al. 1982). Also from clinical studies it is known that the vulnerability to paroxysmal atrial fibrillation is significantly increased in patients with enlarged atria, as determined echocardiographically during sinus rhythm (Henry et al. 1976). These observations are in accordance with the already mentioned multiple wavelet theory of fibrillation, which states that for the continuation of the fibrillatory process a critical minimal number of wavelets must be simultaneously present in a given tissue mass. With a large tissue mass, more wavelets can be accommodated, and thus little chance exists for spontaneous termination of fibrillation. In their mapping studies of fibrillation in intact canine atria, Allesie et al. (1985) observed that a minimal number of 6 simultaneous activation waves was required for fibrillation to be stable, whereas a high chance of cessation of the fibrillatory process existed when the number of wavelets was between 3 and 6. Together with the tissue mass, the total number of impulses which can simultaneously travel through the heart is also determined by the length of the excitation wave. The wavelength of the propagating impulse determines the minimal size of the intramyocardial circuits. Thus, if the wavelength is short, more circulating wavelets can be present in a given tissue mass.

The aim of this study.

According to the wavelength principle, the length of the excitation wave plays a critical role in the initiation and continuation of reentrant arrhythmias. Interventions which shorten the wavelength may be expected to favour the occurrence of these arrhythmias, whereas circumstances which prolong the wavelength would exert an anti-arrhythmic effect. Ideally, this hypothesis should be tested in a model in which manipulation of the wavelength can be directly correlated to the inducibility of reentrant arrhythmias. Furthermore, an intact conscious animal model would be preferable

because it allows measurements under optimal physiological conditions. Since it is known that in canine atria episodes of rapid repetitive activity, atrial flutter and atrial fibrillation can be elicited, we developed a chronically instrumented, conscious dog model in which the length of the atrial excitation wave could be measured. Under a variety of circumstances, we correlated the present values of refractoriness, conduction velocity and wavelength to the induction of various atrial tachy-arrhythmias. We found that the length of the atrial excitation wave is a reliable and constant index of the susceptibility of the atria to arrhythmias like rapid repetitive responses, atrial flutter and atrial fibrillation. Thereby, this model provides a rational and rather simple method to test the efficacy of anti-arrhythmic drugs.

CHAPTER II

A CONSCIOUS DOG MODEL FOR CHRONIC MEASUREMENT OF THE WAVELENGTH IN THE ATRIUM

The purpose of this study was to measure the wavelength of the electrical impulse in different parts of the atrium in conscious dogs and to determine the influence of autonomic transmitters and various cardiac drugs. A chronic dog model offers the opportunity to measure some physiological variables under completely normal conditions and to study the long-term effects of cardiac drugs. In addition, such an animal model has the advantage that fundamental changes in electrophysiological parameters can be directly compared with the inducibility of cardiac arrhythmias.

2.1 Electrodes.

We implanted multiple stimulating and recording electrodes in the atria to measure both refractory period and conduction velocity. Figure 2.1 shows a complete set of electrodes for implantation. In order to measure the wavelength in different areas of the atrium, two recording electrodes were used. The longer electrode, consisting of a double row of 8 platinum electrodes (diameter 1.5 mm, interelectrode distance 12 mm) embedded in silicone (Silastic, Dow Corning), was placed on the bundle of Bachmann. The shorter electrode, containing 7 pairs of contacts (interelectrode distance 8 mm), was sutured to the free wall of either the right or the left atrium parallel to the AV ring. In both recording electrodes the distance between the rows was 8 mm. For stimulation two pairs of silver plates (diameter 7 mm) were used. Finally, two subcutaneous electrodes, one for grounding and one which was used as indifferent electrode, completed the implantation set. In total 36 leads were soldered to a connector (diameter 11 mm, Lemosa), which was fixed in a Teflon ring. Another ring could be screwed on top of it to fix the connector to the skin in the neck.

Figure 2.1: Photograph of a set of implantable electrodes. The set consists of two electrodes: a longer one with two rows of 8 platinum contacts (interelectrode distance 12 mm) to be positioned on the bundle of Bachmann, and a shorter electrode (2×7 contacts, interelectrode distance 8 mm) which could be fixed to either the right or left atrial free wall. The distance between the two rows measures 8 mm in both electrodes. Also two pairs of silver plates (diameter 7 mm) were included in the set to serve as pacing electrodes. The contacts were connected to a plug in a teflon casing, which could be fixed in the skin.

2.2 The implantation procedure.

Nineteen dogs of both sexes and weighing between 30 and 40 kilograms were used for this study. Before the dogs were operated they were accustomed to the laboratory environment and the investigator. After premedication with Hypnorm (0.4 ml/kg) the dogs were anaesthetized with sodium pentobarbital (15 mg/kg). After intubation positive pressure ventilation was applied and anaesthesia was maintained with a 2:1 mixture of oxygen and nitrous oxide.

The thorax was opened by a left intercostal incision between the fourth and fifth rib. After opening of the pericardium the smaller recording electrode was sutured to the free wall of the right (14 dogs) or left atrium (3 dogs), parallel to the AV ring. In one dog, electrodes were

placed on both the right and left atrial free wall. The longer electrode was pulled through the natural tunnel between the atria and the aortic root. The ends of the electrodes were fixed to the tips of the left and right atrial appendage. Because of this anatomic position most of the electrodes were in close contact with Bachmann's bundle. To stimulate the atria two pairs of silver plates were stitched to the tip of the appendages, in close approximation of the first pair of recording electrodes (distance ± 6 mm) on Bachmann's bundle. Figure 2.2 shows a schematic drawing of the position of the electrodes on the heart. A Tygon catheter was inserted in the left atrium to provide an easy access route for drug administration. After loosely closing the pericardium, the thorax was closed and the cables were tunnelled subcutaneously to the neck where the connector was externalized through an incision in the skin. Figure 2.3 gives an X-ray of the dog's thorax after the implantation has been completed.

Figure 2.2: Schematic representation of the position of the electrodes on the heart after implantation. The long electrode is positioned on Bachmann's bundle between the right and left atrial appendage (RAA and LAA). The other electrode is attached to the free wall of either the right or left atrium, parallel to the AV ring. Two pairs of stimulating electrodes (black circles) are fixed to the atrial appendages. (SVC = superior vena cava.)

Figure 2.3: X-ray of the thorax of a dog with implanted electrodes. The two double row electrodes and the pairs of stimulating electrodes are clearly visible. Also the course of the cables and the connector in the neck can be identified.

2.3 The experimental equipment.

In order to make measurements, a cable (36 leads) was plugged into the connector in the neck of the animal. Thirty leads coming from the multiple recording electrodes on Bachmann's bundle and the free wall of the right or left atrium were connected to the positive input of individual amplifiers (bandwidth 2-400 Hz). One lead coming from a subcutaneous plate served as common indifferent electrode and was fed into the negative input of the amplifiers. The four leads going to the two pairs of pacing electrodes were connected to programmable stimulators. A lead from another subcutaneous plate was used for grounding. By means of a patch panel a selection of 16 unipolar recordings could be made for simultaneous display on two 8-channel oscilloscopes (Tektronix 1503N). Two electrograms were selected to feed into two transient recorders (Datalab DL901), from which the activation times of the signals could be read using an interval counter (HP 5308A). The atrium was paced by programmable stimulators, which delivered constant

current square pulses with a duration of 2 milliseconds and a strength of two or four times threshold. For bipolar stimulation one of the pairs of plate electrodes or any pair of recording electrodes could be selected. The atrium was driven with a regular rhythm. After every 15-th impulse one or two independently coupled premature stimuli (stimulus strength 4 times threshold) could be given. A scheme of the experimental set-up is given in figure 2.4.

Figure 2.4: Schematic drawing of the experimental set-up. The leads from the multiple electrodes on the atrium were connected to the experimental equipment by plugging a cable into the connector in the dog's neck. The atrium was paced by programmable stimulators which delivered square pulses of 2 ms duration. The recorded signals were individually amplified and a selection of electrograms was made for simultaneous display on an oscilloscope. After checking the conduction pattern of the impulse, two electrograms were fed into transient recorders. The continuous display of these electrograms, as recorded during a selected time window, allowed measurement of the activation times using an interval counter.

2.4 Evaluation of the chronic dog model.

Time course of the stimulation threshold.

Immediately after the implantation procedure, the stimulus threshold for the point electrodes was between 0.2 and 0.5 milliampere and for the plate electrodes between 1.5 and 2.0 mA. The threshold for the plate electrodes is higher because of the larger electrode surface; consequently, more current is required to generate the same current density. In the upper panel of figure 2.5 the time course of the threshold for stimulation is given for a pair of plate electrodes at the left appendage, a pair of point electrodes at the bundle of Bachmann and a pair of point electrodes at the free wall of the right atrium. The stimulus threshold for the point electrodes at Bachmann's bundle increased gradually to reach a value of 9 mA about eight weeks after implantation. At the free wall of the right atrium the stimulus threshold increased more quickly and reached a value of 9 mA already after six weeks. The threshold of the plate electrodes increased relatively slowly to double from an initial value of 2 mA to about 4 mA in eight weeks. For this reason we preferably used the plate electrodes at the atrial appendages to pace the atrium.

Time course of the amplitude of the recorded electrograms.

In the lower panel of figure 2.5 the amplitude of electrograms recorded from the bundle of Bachmann and the free wall of the right atrium is plotted against time. The recorded amplitude of the electrograms from Bachmann's bundle gradually decreased from about 20 mV immediately after the operation to 6 mV eight weeks later. The electrograms recorded from the free wall of the right atrium showed a quicker decrease in amplitude. Starting at a somewhat lower voltage the quality of the recordings was reduced to about 25% in 4 to 5 weeks.

Figure 2.5: Representative example showing the time dependency of pacing threshold and amplitude of recorded electrograms. The upper panel shows the time course of the stimulation threshold as determined with a pair of plate electrodes (■) and a pair of point electrodes at Bachmann's bundle (▼) or the right atrial free wall (●). Although initially the threshold is higher at the plate electrodes, the degree of increment is much less than with the point electrodes, and after four weeks the threshold is actually lower. The point electrodes on the right atrial free wall showed the fastest increase in stimulation threshold.

The time course of the amplitude of the signals recorded at Bachmann's bundle (▼) and the right atrial free wall (●) is shown in the lower panel. There is an inverse relationship with the course of the stimulation threshold, the signals from the right atrial free wall exhibiting the fastest decay in amplitude. These time dependent changes in stimulation threshold and recorded amplitude allowed reliable measurements during a period of 6 to 8 weeks.

Structural changes of the atria due to the implanted electrodes.

Although for implantation materials were used which are known to cause minimal tissue reaction, the presence of the electrodes on the surface of the atria did not remain unnoticed to the heart. Histological examination of the atria was performed at the end of an 8 weeks' period. Figure 2.6 shows two photomicrographs of sections of the atrial myocardium below the recording electrodes. One was taken from Bachmann's bundle (left panel), the other from the right atrial free wall (right panel). In both cases the electrode has left a clear imprint in the epicardial surface. A fibrotic

DEVELOPMENT OF FIBROTIC LAYER

BACHMANN BUNDLE

RIGHT ATRIAL FW

Figure 2.6: Photomicrographs of sections of the atrial myocardium below an electrode at the Bachmann bundle (left) and at the right atrial free wall (right) as made two months after implantation. Magnification 23x, HE and aaan staining. At both sites the electrode has left a clear pit in the epicardial surface. A sharply demarcated, fibrotic layer (dark) has been formed between the electrode and the normal myocardium. This layer was about twice as thick at the right atrial free wall. This difference in thickness probably is the cause of the different time courses of the stimulation threshold and amplitude of the recorded signals at the two sites.

layer (dark in the photograph) of various thickness has developed between the electrode and the normal myocardium. There is a striking difference in the amount of tissue reaction in the two different areas, the dark fibrotic layer being about twice as thick in the section from the right atrial free wall compared to the section taken from the Bachmann bundle. This might be explained by the fact that the free wall of the atrium is much more in motion and therefore experiences a greater scraping effect of the electrodes.

The growing layer of fibrosis between the electrodes and the myocardium forms an increasing electrical resistance, which explains the increase in stimulus threshold and the decrease in the amplitude of the recorded electrograms. In the right atrium both the elevated stimulus threshold and the low amplitude of the electrograms made it impossible to accurately measure refractory period and conduction velocity after a period of four weeks. The slower development of fibrosis under the bundle of Bachmann electrode allowed measurements during approximately two months.

Time course of refractory period, conduction velocity and wavelength.

During the period a chronic animal model is used, control measurements should stay constant. If there is a time dependent change in any of the measured parameters, the determination of long term drug effects is not reliable. Figure 2.7 shows the time course of control measurements of refractory period, conduction velocity and wavelength during a regular rhythm, as measured in one dog in the left part of Bachmann's bundle. The measurements were carried out for a period of eight weeks. After a short post-operative stabilization phase the values of refractory period, conduction velocity and wavelength all remained fairly constant, the range of RP being 102-110 ms, of CV 125-133 cm/s and of WL 13.2-14.2 cm. Table 2.1 gives the control values of RP and CV measured in the 19 individual dogs at four atrial areas during the total observation period of maximally 2 months. Although some dogs exhibited a higher degree of fluctuation in the control values as compared to the example of figure 2.7, the individual variation coefficients for RP and CV at the four different atrial sites never exceeded 7%, while the mean coefficients of all dogs varied only from 3% to 5%. Furthermore, no time dependent trend in the control values could be observed. This stability of the control values made it possible to carry

out reliable measurements for about two months in most dogs. However, in some dogs one or two measuring sites could not be used because of high stimulation thresholds or poor quality recordings already immediately or soon after implantation. Post mortem examination showed that this was caused by poor contact between electrodes and myocardium.

Figure 2.7: Refractory period, conduction velocity and wavelength determined at one site as a function of time. Results of one dog are given. After a period of relative instability immediately postoperatively, the values remained fairly constant for two months, RP ranging from 102-110 ms, CV from 125-133 cm/s, and WL from 13.2-14.2 cm. This allowed us to carry out reliable measurements during this period. Control values of RP and CV of all dogs are given in table 2.1.

Table 2.I Control Values (and ranges) of Refractory Period and Conduction Velocity during regular pacing (350 ms interval) as measured at 4 different atrial sites during the total observation period.

<u>dog</u> <u>nr</u>	<u>Bachmann Bundle Right</u>		<u>Bachmann Bundle Left</u>	
	Refractory Period (ms)	Conduction Velocity (cm/s)	Refractory Period (ms)	Conduction Velocity (cm/s)
1			109 _± 4 (103-116)	125 _± 4 (118-128)
2			118 _± 3 (115-124)	131 _± 3 (128-136)
3	134 _± 4 (128-140)	137 _± 5 (130-143)	111 _± 4 (105-116)	117 _± 4 (113-123)
4	143 _± 3 (139-145)	114 _± 5 (107-120)	115 _± 4 (111-120)	112 _± 7 (105-122)
5	125 _± 4 (118-130)	121 _± 1 (120-122)	109 _± 3 (106-115)	123 _± 4 (118-128)
6	131 _± 5 (124-137)	141 _± 2 (137-145)	98 _± 3 (93-102)	120 _± 1 (117-121)
7	136 _± 3 (132-139)	133 _± 5 (123-138)		
8	136 _± 3 (133-140)	153 _± 3 (150-159)	109 _± 3 (105-114)	123 _± 7 (110-133)
9	134 _± 6 (128-144)	124 _± 3 (121-128)	117 _± 3 (112-122)	123 _± 2 (118-125)
10			111 _± 4 (106-115)	124 _± 3 (118-128)
11	136 _± 4 (130-140)	145 _± 1 (143-146)	110 _± 4 (104-114)	139 _± 3 (136-143)
12	130 _± 3 (126-132)	134 _± 1 (133-136)	116 _± 3 (113-120)	121 _± 3 (118-125)
13			121 _± 6 (114-128)	131 _± 6 (125-143)
14	144 _± 4 (139-151)	140 _± 5 (133-146)	104 _± 6 (96-115)	132 _± 2 (130-136)
15	126 _± 4 (119-132)	139 _± 4 (133-143)	111 _± 8 (99-121)	132 _± 3 (128-136)
16	134 _± 5 (127-140)	137 _± 4 (133-143)	113 _± 3 (108-117)	128 _± 5 (118-133)
17	125 _± 2 (122-127)	128 _± 4 (120-133)	107 _± 3 (102-110)	131 _± 3 (125-133)
18	142 _± 4 (136-147)	131 _± 6 (125-140)	125 _± 6 (114-133)	131 _± 6 (125-140)
19	139 _± 4 (135-147)	125 _± 4 (119-133)	112 _± 2 (109-115)	123 _± 1 (122-124)

Table 2.I continued.

<u>dog</u> <u>nr</u>	<u>Free Wall Right Atrium</u>		<u>Free Wall Left Atrium</u>	
	Refractory Period (ms)	Conduction Velocity (cm/s)	Refractory Period (ms)	Conduction Velocity (cm/s)
1	142 $\pm$ 5 (136-147)	116 $\pm$ 4 (112-120)		
2				
3	128 $\pm$ 5 (121-135)	146 $\pm$ 1 (145-149)		
4	134 $\pm$ 5 (126-140)	119 $\pm$ 3 (114-121)		
5	128 $\pm$ 5 (122-136)	137 $\pm$ 5 (133-143)		
6	118 $\pm$ 5 (110-125)	109 $\pm$ 3 (105-114)		
7	123 $\pm$ 2 (119-125)	115 $\pm$ 2 (113-117)		
8	120 $\pm$ 4 (115-124)	129 $\pm$ 4 (121-133)		
9	125 $\pm$ 3 (122-128)	115 $\pm$ 2 (114-118)		
10	123 $\pm$ 3 (120-126)	120 $\pm$ 5 (114-129)		
11	131 $\pm$ 6 (123-140)	131 $\pm$ 2 (129-133)		
12	126 $\pm$ 3 (122-131)	119 $\pm$ 1 (118-121)		
13	113 $\pm$ 7 (102-120)	133		
14	132 $\pm$ 5 (128-141)	110 $\pm$ 2 (108-114)		
15	129 $\pm$ 5 (123-136)	111 $\pm$ 6 (105-119)		
16			109 $\pm$ 5 (104-118)	129 $\pm$ 4 (125-133)
17			121 $\pm$ 5 (113-128)	138 $\pm$ 4 (133-143)
18			110 $\pm$ 3 (107-114)	136 $\pm$ 2 (133-138)
19	118 $\pm$ 4 (111-124)	123 $\pm$ 3 (119-128)	104 $\pm$ 4 (97-107)	122 $\pm$ 3 (118-125)

2.5 Measurement of the conduction velocity.

In order to make accurate measurements of the conduction velocity of the cardiac impulse, several precautions have to be taken to prevent systematic errors. The first recording electrode should be at a sufficiently large distance from the stimulus site to prevent direct stimulation of the myocardium by the stimulus, thus ensuring that myocardial propagation has actually started at the first recording site. Furthermore, one must know the exact pathway followed by the depolarization wave. Also the conduction along the followed pathway must be uniform: there should be no distinct areas of conduction delay or block. If only two recording electrodes are used, one at the start and one at the end of the presumed pathway, it is impossible to check the impulse's route, making it hazardous to calculate a reliable conduction velocity from the difference in activation time of the two electrodes. Using a single row of electrodes, uniformity in conduction can be checked because areas of depressed conduction will be detected by locally delayed activation times. But even if conduction velocity is constant along the row of recording electrodes, one still cannot be certain whether the wave front propagates parallel to the electrodes. If the direction of propagation is oblique to the row of recording electrodes, conduction velocity can be seriously overestimated. To meet the requirement to check both uniformity and direction of conduction we used a double row of recording electrodes. Conduction is assumed to occur parallel to the electrodes if the electrodes of each pair are activated simultaneously. In figure 2.8 the activation along a double row of electrodes is shown for a basic and an early premature beat. The stimulus site is at the beginning of the row. The distance between pacing site and the first recording electrodes varied from 5-8 mm in our experiments. In each tracing the two electrograms of an electrode pair are superimposed. During basic rhythm, the conduction time from the first to the last electrode pair was 46 ms. Figure 2.8 clearly shows that the above stated criteria are fulfilled: 1. propagation of the impulse is parallel to the electrode rows, because the electrograms from the paired electrodes are simultaneous; 2. there is uniform conduction because the activation time differences between successive electrodes are about equal. This also indicates that there is no direct stimulation of the myocardium below the proximal electrodes by the

Figure 2.8: Conduction of regular and earliest premature beat along the double row electrode. The stimulus site was close (+6 mm) to the first recording electrodes. Superimposed electrograms recorded at electrode pairs on the two rows and activation maps of the electrode are shown. Electrograms recorded at the paired electrodes are almost simultaneously, and thus the isochrones can be drawn perpendicular to the long axis of the electrode. Therefore, it may be concluded that the impulse propagated parallel to the electrode. Conduction was also uniform, since the activation time differences between adjacent electrodes were fairly equal, resulting in equidistant 10 ms isochrones. These observations are valid for the conduction of both the regular and the early premature impulse, although the latter propagated more slowly (conduction time 46 versus 68 ms). Because propagation of the activation front is uniform and parallel to the long axis of the electrode, calculation of the conduction velocity from the conduction time and the distance between the first and last recording electrode is allowed.

external stimulus. The same conclusions hold true for the premature beat. Although it is conceivable that during a premature beat the impulse is conducted differently and activates the bundle obliquely or that distinct areas of conduction delay arise, the photograph illustrates that this is not the case. Also during the premature beat the two electrodes of a pair are activated simultaneously and, although the speed of propagation of the impulse front has slowed down, conduction remains uniform. Thus, in either case the isochrones in the activation map are perpendicular to the long axis of the electrode and equidistant.

Figure 2.9: As figure 2.8, but now the propagation of two impulses out of a long series during the maximal pacing rate is shown. It may be concluded that also during this very rapid rhythm (110 ms interval) conduction is still uniform and parallel to the long axis of the electrode. The conduction time from first to last electrode was 59 ms during this rhythm.

Even during pacing at the maximal rate the impulse runs parallel to the electrode without discrete areas of impaired conduction, as shown in figure 2.9.

When the pacing rate was increased above the maximal rate at which every stimulus still resulted in an impulse propagated to the end of the bundle, two different responses were observed: 1. failure in eliciting a depolarization wave at the stimulus site with every stimulus, or 2. conduction block of the impulse somewhere along the bundle. During control the former possibility was observed most frequently, whereas under circumstances which strongly affected conduction, e.g. high doses of lidocaine or propafenone, conduction block occurred in many instances. This is quite distinctive from the situation in isolated rabbit atrial preparations in which a further increase of the pacing rate always caused the impulse to block along the myocardial bundle below the recording electrodes (Smeets 1983). The fact that this happened in the intact model only if conduction was hampered by drug interventions might indicate that in the tissue bath conditions for impulse propagation are not as optimal as in the physiological situation.

2.6 Measurement of the refractory period.

Bipolar stimulation of the atrium was carried out by using either a pair of point electrodes or a pair of silver plates at the tip of the atrial appendage. The refractory period was determined by means of programmed electrical stimulation using the extrastimulus technique.

Stimulus intensities varying from 2 to 6 times threshold have been used to measure the refractory period in the canine atrium (Andrus et al. 1930, Mendez et al. 1956, Alessi et al. 1958). Since the stimulus strength may seriously affect the shortest possible coupling interval we determined the relationship between stimulus strength and refractory period in each dog before the actual measurements were carried out. A typical example of this relationship is shown in figure 2.10. The basic pacing interval was 350 ms.

Figure 2.10: Relationship between stimulus intensity and refractory period (RP), as determined in one dog. Threshold was measured during a regular rhythm with a pacing interval of 350 ms. Small changes in stimulus intensity resulted in a profound decrease of the minimal coupling interval. A zone of supranormal excitability can be observed between coupling intervals of 175 and 300 ms. At higher stimulus intensities the curve becomes progressively steeper, and an increase of the stimulus strength to more than 3x threshold does not affect the RP anymore. Because in all dogs a similar course of the strength-interval curve was found, we always used extra-stimuli with a strength of 4 times threshold for the determination of the refractory period.

It can be observed that minimal changes in strength of the extrastimulus can profoundly decrease the shortest possible coupling interval, and also a zone of slight supranormal excitability can be identified between coupling intervals of 175 and 300 ms (Hoffmann and Cranefield 1960). At higher stimulus intensities the curve becomes progressively steeper and from 3 to 4 times threshold the minimal coupling interval is hardly affected anymore. Therefore extrastimuli were always applied with a strength of four times threshold.

The measured value of the refractory period also depends on which criterium for refractoriness is used. On the basis of the definitions of refractoriness (Hoffmann and Cranefield 1960), we distinguished the following definitions for the atrial refractory period:

- the absolute refractory period (ARP): the longest coupling interval between a basic (S1) and a premature (S2) stimulus of high intensity during which no propagated atrial response can be evoked.
- the effective refractory period (ERP): the shortest coupling interval between S1 and S2 at which an atrial depolarization can be elicited.
- the functional refractory period (FRP): the shortest possible interval between two atrial depolarization waves (A1-A2).

The FRP strictly represents the minimal coupling interval which can physiologically occur, but measurement of the ERP is more convenient. For this reason we determined to what extent the values obtained by the two methods differed in five dogs. A representative example of the relationship between ERP and FRP during a regular rhythm (pacing interval 350 ms) is given in figure 2.11. The A1-A2 interval, measured at the recording electrode nearest to the stimulus site, is plotted as a function of the S1-S2 interval. At longer coupling intervals the A1-A2 interval equals the S1-S2 interval. At the left end of the curve however, a further shortening of the S1-S2 interval first leads to an increase of the A1-A2 interval and finally it remains constant. This difference between the S1-S2 and the A1-A2 interval at short coupling intervals may be due to an increased latency between stimulation and activation at the stimulation site. Because the shortest S1-S2 interval did not match exactly the minimal interval between two atrial depolarization waves, the refractory period was deter-

Figure 2.11: Relationship between S₁-S₂ interval and A₁-A₂ interval determined during pacing at an interval of 350 ms. A typical example of one dog is shown. The A₁-A₂ interval, as measured at the recording electrode nearest to the stimulus site, is plotted as a function of the S₁-S₂ interval. In the prematurity range from 135-300 ms the A₁-A₂ interval equals the S₁-S₂ interval. A decrease of the S₁-S₂ interval from 135 to 120 ms results in an increase of the A₁-A₂ interval from 135 to 145 ms. A further decrease of the S₁-S₂ interval does not change the A₁-A₂ interval anymore. Because the shortest S₁-S₂ interval (Effective Refractory Period) does not represent the shortest interval between two successive atrial impulses, we always measured the Functional Refractory Period (shortest possible A₁-A₂ interval).

mined by measuring the shortest possible A₁-A₂ interval, i.e. the functional refractory period.

The functional refractory period is thus defined as the shortest possible A₁-A₂ interval, measured at the recording electrode nearest to the stimulus site at a stimulus strength of four times diastolic threshold.

2.7 Measurement of the wavelength.

The wavelength of the cardiac impulse is defined as the distance travelled by the impulse during the time the myocardium restores its excitability. It can be calculated by multiplying the conduction velocity by the functional refractory period.

$$\text{WAVELENGTH (cm)} = \text{CONDUCTION VELOCITY (cm/s)} \times \text{REFRACTORY PERIOD (s)}$$

The experimental protocol for electrical stimulation included measurements of refractory period, conduction velocity and wavelength at different pacing rates, the induction of single and double premature beats, and incremental pacing to the highest possible pacing rate. The stimulus duration was 2 ms, the stimulus intensity 2 x threshold for basic beats (S1) and 4 x threshold for extrastimuli (S2 and S3). Determination of stimulus thresholds was regularly repeated, but they became significantly higher only at pacing intervals below 150-175 ms, the maximal increase being 200-300%.

The wavelength of a regular rhythm.

In order to calculate the wavelength of a regular rhythm, the conduction velocity and the refractory period of a basic impulse must be measured *simultaneously*. The left panel of figure 2.12 shows the stimulation protocol for such a measurement. During a regularly driven rhythm (350 ms interval) a single premature stimulus was given after every 15th beat. The last basic beat and the earliest premature impulse are displayed. S1 denotes the last basic stimulus, A1 the atrial response to S1, S2 the premature stimulus and A2 the response to S2. The upper electrogram was recorded at an electrode next to the stimulus site, the lower electrogram at an electrode at the end of the bundle at a distance of 60 mm. The time the impulse needed to travel from the first to the last electrode was 46 ms, and therefore the conduction velocity was 60 mm/46 ms. During this rhythm the shortest A1-A2 interval was 108 ms. Consequently, the wavelength measured $60 \text{ mm}/46 \text{ ms} \times 108 \text{ ms} = 14.1 \text{ cm}$.

Figure 2.12, left panel: Calculation of the wavelength of a regular impulse. The upper tracing was recorded next to the stimulus site, the lower tracing at the end of the row of electrodes at a distance of 60 mm. After a series of 15 basic impulses, a premature impulse is elicited. S_1 and S_2 denote the last basic and the premature stimulus respectively, A_1 and A_2 the atrial responses to these stimuli. Conduction time of the basic impulse from the first to the last recording electrode was 46 ms. The shortest A_1 - A_2 interval was 108 ms. Thus the wavelength can be calculated to be $60 \text{ mm}/46 \text{ ms} \times 108 \text{ ms} = 14.1 \text{ cm}$.

Right panel: Determination of the wavelength of a premature impulse. The conduction time of the premature impulse (A_2) from the first to the last recording electrode (distance 60 mm) was 76 ms. A second premature impulse (A_3) was elicited to determine the shortest possible A_2 - A_3 interval, which was 84 ms. Thus in this example the wavelength of the premature impulse measured $60 \text{ mm}/76 \text{ ms} \times 84 \text{ ms} = 6.6 \text{ cm}$.

The wavelength of a premature impulse.

By adding a second extrastimulus to the stimulation protocol (S_1 - S_2 - S_3) the wavelength of a premature beat can be calculated in an analogous manner as the wavelength of a basic beat. In the right panel of figure 2.12 the second earliest premature beat is also shown. The conduction time of the first premature impulse (A_2) is 76 ms. The refractory period of A_2 , the shortest possible A_2 - A_3 interval is 84 ms. So the wavelength of the first premature beat is 6.6 cm ($60 \text{ mm}/76 \text{ ms} \times 84 \text{ ms}$).

The wavelength at high pacing rates.

The fastest pacing rate can be determined by progressively shortening the pacing interval (S_1 - S_1 - S_1 ...) until the impulse blocks at the stimulus site or in the bundle. The maximal pacing rate (F_{max}) is defined as the

shortest possible pacing interval at which every impulse elicits a propagated response in the atrium. The wavelength of Fmax can be determined in the same way as during a slow regular rhythm.

2.8 The induction of arrhythmias.

After a couple of days when the dogs had recovered from surgery and had got used to the laboratory environment, measurements could be easily made during several hours while the dogs were lying quietly on the floor. In this drowsy state, arrhythmias could be often induced by single premature stimuli. We distinguished three classes of arrhythmias:

1. Rapid Repetitive Responses (RRR), a series of no more than 5 premature beats immediately following the induced premature impulse with a cycle length shorter than 150 ms. 2. Atrial Flutter (AFI): a regular rapid rhythm with monomorphic electrograms and cycle length between 85 and 150 ms and a regular ventricular response. 3. Atrial Fibrillation (AFib): an irregular extremely rapid rhythm with polymorphic electrograms and an irregular ventricular response.

2.9 Statistical analysis.

Results are expressed as the mean $\pm$ standard deviation. The statistical significance of differences between the control and the various drug groups was determined by the unpaired Student's t test. Although in each dog control measurements were repeated before the testing of the different drugs, only one control experiment per animal was represented in the control group in order to have comparable group sizes for control and drug studies. This was necessary for a proper use of linear discriminant analysis as presented in chapter VI.

Linear discriminant analysis.

In this study it was our goal to compare the relative importance of refractory period, conduction velocity and wavelength in the induction of different reentrant arrhythmias. Therefore we wanted to determine which of the three electrophysiological parameters distinguished best between the

various types of atrial response. Linear discriminant analysis is a very useful method for this purpose. This statistical procedure utilizes one or more variables to derive optimal polynomial functions that separates a group of observations into two or more subpopulations. We used this method to determine the predictive value of one variable (RP, CV or WL) for the occurrence of four types of responses (No Arrhythmias, Rapid Repetitive Responses, Atrial Flutter and Atrial Fibrillation). The analysis results in four optimal classification functions. With those functions the probability is calculated that with a given value for RP, CV or WL the response to a premature beat will be either No Arr, RRR, AF1 or AFib. By comparing this computed classification to the actual events, the predictive power of each variable for the initiation of arrhythmias can be calculated (Klecka 1983).

Another advantage of this statistical analysis is that on the basis of those discriminant functions also the critical values of RP, CV and WL for the occurrence of arrhythmias can be determined. Calculation of the points of intersection between the respective discriminant functions gives the values of RP, CV or WL which render optimal discrimination between the subsequent subpopulations. In this way we defined the critical values of RP, CV and WL for the induction of RRR, AF1 and AFib.

Sensitivity and specificity of RP, CV and WL for the initiation of RRR, AF1 or AFib were also calculated by discriminant analysis. For this purpose the analysis was used for only two subpopulations: No Arrhythmias and the arrhythmia for which sensitivity and specificity were to be determined. The percentage correct classification in the arrhythmia group (test correctly "positive") is the sensitivity of the variable for the arrhythmia in question, whereas the specificity (test correctly "negative") is given by the percentage correct classification in the No Arrhythmia group.

CHAPTER III

PROGRAMMED ELECTRICAL STIMULATION, MEASUREMENT OF WAVELENGTH AND THE INDUCTION OF ATRIAL ARRHYTHMIAS

Intra-atrial reentry is considered as an important pathophysiological mechanism for atrial arrhythmias (Allessie et al. 1977, 1984, 1985, Boineau et al. 1980, Boyden et al. 1981, 1984, Page et al. 1983, Okumura et al. 1984, Frame et al. 1986, Olshansky et al. 1986). According to our hypothesis, a short wavelength of the electrical impulse should enhance the chances for both the initiation and persistence of reentrant circuits. In a number of clinical studies using programmed electrical stimulation, it was shown that both a high driving rate and a short coupling interval of extrasystoles make the atria more susceptible to tachy-arrhythmias like rapid atrial firing, atrial flutter and atrial fibrillation (Haft et al. 1968, Wyndham et al. 1977, Engel et al. 1978, Watson et al. 1980, Michelucci et al. 1982, Simpson et al. 1982, Cosio et al. 1983). It is well known that rapid pacing and early premature beats shorten the atrial refractory period and depress intra-atrial conduction. These changes in electrophysiological parameters will shorten the wavelength. However, it is not known to what extent, because in none of the studies the actual conduction velocity has been measured. In isolated strips of rabbit atrium in which the refractory period and the conduction velocity of an impulse were measured simultaneously, it was shown that both early premature beats and rapid pacing cause a decrease of the length of the excitation wave of 45% and 33%, respectively (Smeets et al. 1986). We used chronically instrumented dogs to determine the effects of changes in rate and rhythm on the atrial wavelength under completely physiological circumstances. Moreover, this experimental model allowed a direct correlation between changes in basic electrophysiological properties and the induction of atrial arrhythmias. Because inhomogeneity in these properties may be affected by cardiac rate and rhythm, we also studied their spatial dispersion by measuring the refractory period, conduction velocity and wavelength at multiple sites of the right and left atrium.

3.1 Experimental protocol.

In 19 dogs electrodes were implanted on the bundle of Bachmann and on the free wall of either the right or the left atrium and the effects of changes of rate and rhythm on the wavelength were examined. Because of poor quality of the local electrograms or high stimulus thresholds soon after implantation, some measuring sites could not be used in several dogs. Consequently, the number of observations for the various measuring sites differ. In all dogs the protocol for electrical stimulation included the induction of single and double premature beats during a regularly driven rhythm. During slow pacing (350 ms interval) the wavelength of single premature impulses was determined at the following coupling intervals: 300, 250, 200, 175, 150 ms and down to the shortest possible coupling interval in steps of 10 ms. Furthermore, the effect of regular pacing at increasing rates was studied. The wavelength of regular rhythms was measured at pacing intervals of 300, 250, 200, 175 and 150 ms and from 150 ms down to the shortest possible pacing interval in steps of 10 ms.

The wavelength was measured at four different parts of the atria (the right and left part of Bachmann's bundle, and the right and left atrial free wall). In addition, the refractory period was measured at twenty-two sites along the Bachmann bundle and on the free wall of either the right or the left atrium.

Linear discriminant analysis was applied to determine the predictive power and critical values of refractory period, conduction velocity and wavelength for the induction of rapid repetitive responses (RRR), atrial flutter (AFI) and atrial fibrillation (AFib).

3.2 Results

The effects of heart rate on the wavelength.

In figure 3.1 the relation between the pacing interval during a regular rhythm and refractory period, conduction velocity and wavelength as determined in the left part of Bachmann's bundle is shown. The mean values and standard deviations of 13 dogs are plotted. At a slow pacing rate (350 ms interval) the refractory period at the left auricle was 114 ± 7 ms, the

Figure 3.1: The effect of the pacing interval on the wavelength of a regularly driven impulse as determined in the left part of Bachmann's bundle. The mean and standard deviation ($N=13$) of the refractory period, conduction velocity and wavelength are plotted as a function of the pacing interval. Shortening of the pacing interval from 350 to 200 ms had no significant effect on the three variables. A further decrease of the pacing interval caused a progressive decrease of both refractoriness (-22%) and conduction velocity (-30%), resulting in a wavelength shortening from 14.5 to 7.9 cm (-46%).

Figure 3.2: The effect of the degree of prematurity of extrasystoles on refractory period, conduction velocity and wavelength. Mean values and standard deviation (N=18) as measured in the left part of the Bachmann bundle are plotted. Premature beats with coupling intervals longer than 250 ms did not alter these variables. Further shortening of the coupling interval resulted in a progressive shortening of the wavelength from 14.5 to 6.6 cm (-55%), due to a combined decrease in refractoriness (-30%) and conduction velocity (-35%).

conduction velocity 127 ± 10 cm/s and the wavelength 14.5 ± 1.7 cm. Decreasing the pacing interval from 350 ms to 200 ms did not result in any significant change of the three electrophysiological parameters. Further shortening of the pacing interval down to the fastest possible pacing rate resulted in a progressive shortening of the refractory period and a gradual depression of the conduction velocity. At the shortest possible pacing interval (110 ms) RP had shortened to 89 ± 5 ms (-22%) and CV had decreased to 89 ± 14 cm/s (-30%). Because of this concomitant decrease of refractoriness and conduction velocity the wavelength at the fastest pacing rate was reduced by 46% to 7.9 ± 1.2 cm.

The effects of premature beats on the wavelength.

The effects of single premature beats elicited during a slow regular rhythm (350 ms interval) on refractory period, conduction velocity and wavelength are shown in figure 3.2. Mean values and standard deviations of measurements performed in the left part of Bachmann's bundle (N=18) are plotted. The induction of a late premature beat (coupling interval 250-350 ms) did not affect any of the parameters. At coupling intervals shorter than 250 ms RP decreased progressively from 114 ± 7 to 80 ± 7 ms at the shortest possible coupling interval (-30%). Also the conduction velocity showed a progressive decrease from 127 ± 10 to 82 ± 6 cm/s (-35%). Because of this combined decrease in refractoriness and conduction velocity, the wavelength of the earliest coupled impulse shortened by as much as 55% to 6.6 ± 0.5 cm.

Spatial dispersion in wavelength.

The wavelength measured at one site of the atrium does not necessarily represent the wavelength in other parts of the atrium. Local differences in refractoriness and conduction velocity will lead to a certain spatial dispersion of the wavelength. In 13 dogs we measured the refractory period at a total of 22 different sites located at the free wall of the right and left atrium and along the bundle of Bachmann. The mean values and a histogram are given in figure 3.3. During normal rhythm (regular pacing with an interval of 350 ms, panel A), there were marked differences in local refractory period between different parts of the atria. In the free wall of the right atrium, only a slight spatial dispersion in refractoriness ex-

SPATIAL DISPERSION OF REFRACTORINESS

Figure 3.3: Spatial dispersion of refractoriness in the atrium during different rates and rhythm as measured along Bachmann's bundle (N=13 dogs) and in the free wall of the right (N=10) and left atrium (N=4). The numbers in the maps indicate the mean refractory period at that site. Next to the maps the related histograms of the distribution of local periods are given. In all situations, differences in local RP were only slight in both the right and left atrial free wall, whilst a marked shortening of RP along Bachmann's bundle from right to left was found. During normal rhythm (pacing interval 350 ms, panel A) the maximal difference in RP between the right and left atrium was 26 ms. An early premature beat (panel B) caused a general shortening of the RP by 20-30%, resulting in a leftward shift of the histogram. Also rapid pacing caused (panel C) an uniform yet smaller decrease of refractoriness. Because the width of the three histograms does hardly differ, it may be concluded that the absolute dispersion in RP is not changed by these variations of rate and rhythm.

isted, the difference between the shortest and longest refractory period being no more than 6 ms (122-128 ms). However along the bundle of Bachmann significant differences in refractoriness were measured. In all dogs (N=13) a consistent shortening of the local refractory period was found from the right (133 ms) to the left atrium (107 ms). The free wall of the left atrium again showed uniform refractoriness (maximal difference 10 ms). This systematic transition in duration of refractoriness resulted in a maximal difference in refractory period of 26 ms between the right and the left atrium.

During premature beats, the dispersion of the refractory period showed the same pattern (panel B). However, because all refractory periods were shortened by 25-30%, a general shift of the histogram to the left can be noted. The maximal difference in refractoriness between the right (99 ms) and the left (79 ms) atrium during the earliest premature beat was 20 ms.

Since the degree of spatial inhomogeneity in atrial refractoriness might be affected by heart rate (Han et al. 1966), we repeated these measurements during rapid pacing (interval 110-130 ms). As can be seen in panel C of figure 3.3, rapid pacing caused an uniform decrease of the duration of the refractory period. The systematic change in refractory period along Bachmann's bundle remained present during rapid pacing, the maximal difference in RP between the right (110 ms) and the left (88 ms) atrium being 22 ms.

During slow regular pacing, conduction velocity did not vary much at the different areas of the atria. However, during premature beats the speed of propagation showed more local variation. An example is given in figure 3.4. A series of electrograms as recorded along the bundle of Bachmann during a regular and an early premature beat is shown. In panel A the bundle was activated from right to left (stimulating electrodes at the tip of the right appendage). In panel B the activation was from left to right (pacing at left appendage). Conduction of the basic impulse was uniform and similar in either direction (138 and 133 cm/sec). This was not true for premature impulses. Although still uniform, early premature impulses propagated much slower in a left to right than in a right to left direction (79 versus 109 cm/sec). Thus premature beats caused spatial inhomogeneities in conduction velocity.

CONDUCTION ALONG BACHMANN'S BUNDLE

Figure 3.4: Conduction of regular and early premature beats (EPB) along Bachmann's bundle with pacing at the right (panel A) or the left auricle (panel B). Recordings of one of the two rows of electrodes on the bundle are shown (interelectrode distance 12 mm). In both directions a regular impulse is propagated uniformly and at the same speed. The conduction of the earliest premature beat, although still uniform, is much slower in a left to right direction (79 cm/s) than vice versa (109 cm/s).

As a consequence of local differences in refractoriness and conduction velocity also the wavelength varied in different parts of the atria. We determined the effects of shortening of the coupling interval of extra-systoles on the wavelength at four different areas (right and left part of Bachmann's bundle, right and left atrial free wall). In figure 3.5 the local differences in RP, CV and WL are plotted for premature beats of various prematurity. During a normal rhythm (coupling interval 350 ms) the longest wavelength (17.7 cm) was found in the right part of Bachmann's bundle, whereas in the other three areas values from 14.5 cm to 15.2 cm

Figure 3.5: The effects of premature beats on the wavelength in four different areas of the atrium: right (■, N=15) and left (●, N=18) part of Bachmann bundle and the free wall of the right (▼, N=15) and left (★, N=4) atrium. At all sites increasing the prematurity of extrasystoles caused a progressive shortening of the wavelength. The already existing dispersion in wavelength during a normal rhythm (right end of curves: from 14.5 cm at the left to 17.7 cm at the right side of Bachmann's bundle) is augmented by early premature impulses (wavelength ranging from 6.6 to 10.7 cm at the left and right part of Bachmann's bundle respectively).

Table 3.1

The effects of variations in rate and rhythm on Refractory Period, Conduction Velocity and Wavelength at four different atrial sites.

	N	Regular Rhythm			Earliest Premature Beat			Maximal Pacing Rate		
		RP (ms)	CV (cm/s)	WL (cm)	RP (ms)	CV (cm/s)	WL (cm)	RP (ms)	CV (cm/s)	WL (cm)
BB Right	15	133 +7 -	133 +12 -	17.7 +1.7 -	99 +7 -	107 +13 -	10.7 +1.7 -	106 +8 -	115 +13 -	12.3 +2.0 -
BB Left	18	114 +7 -	127 +10 -	14.5 +1.7 -	80 +7 -	82 +6 -	6.6 +0.5 -	89 +5 -	89 +14 -	7.9 +1.2 -
FW Right	15	124 +9 -	123 +13 -	15.2 +1.5 -	92 +7 -	83 +8 -	7.6 +1.0 -	100 +7 -	95 +16 -	9.5 +2.0 -
FW Left	4	111 +7 -	132 +9 -	14.7 +1.9 -	81 +6 -	95 +7 -	7.7 +0.7 -	88 +4 -	105 +6 -	9.4 +0.7 -

BB Right = Right Part Bachmann Bundle

BB Left = Left Part Bachmann Bundle

FW Right = Right Atrial Free Wall

FW Left = Left Atrial Free Wall

RP = Refractory Period

CV = Conduction Velocity

WL = Wavelength

were measured. The long wavelength in the right part of Bachmann's bundle resulted from the fact that the highest values of both refractory period and conduction velocity were found in this part of the atrium. Although a shortening of the coupling interval caused a gradual decrease in RP and CV in all four areas, these variables were relatively less affected in the right part of Bachmann's bundle because the minimal coupling interval which could be attained was longest at that site. Consequently, during early premature beats spatial differences in WL were even more pronounced. The shortest wavelength was found at the left part of Bachmann's bundle (6.6 cm). In the free wall of the right atrium the WL of a premature beat was 7.6 cm, in the left atrium 7.7 cm, whereas the longest wavelength (10.7 cm) was again located at the right part of the bundle of Bachmann.

In table 3.I the effects of heart rate and prematurity on the different areas of the atria are summarized. It shows that also during rapid pacing the shortest wavelength is found in the left part of Bachmann's bundle.

The induction of arrhythmias.

During programmed atrial stimulation, arrhythmias could be induced with single premature stimuli. Despite the induction of Rapid Repetitive Responses (RRR), Atrial Flutter (AFI) or Atrial Fibrillation (AFib), the wavelength of the premature impulse could be measured in the normal way. This was possible because the spontaneous A3 impulse arose later than the earliest A3 impulse as induced by an early S3 stimulus. The type of atrial response to extrasystoles with varying prematurity was very reproducible in each experiment. However the duration of the sustained arrhythmias did vary considerably (from several seconds to maximally several hours, on an average of 3 minutes). Figure 3.6 shows the different types of arrhythmias that were induced by extrasystoles with varying prematurity. The capitals at the tracings (right panel) correspond with the zones of prematurity in the curves of the left panel. Premature stimuli with long coupling intervals (>175 ms, panel A) only elicited single premature responses after which sinus rhythm resumed. Shorter coupled extrasystoles (coupling interval 135-175 ms, panel B) were followed by a short series of rapid repetitive responses (RRR). Early premature stimuli (coupling interval 125-135 ms, panel C) sometimes resulted in a longer or shorter paroxysm of atrial flutter. Premature stimuli given in a narrow range immediately after the

Figure 3.6: Example of the atrial response to premature stimuli (S_2) elicited in the left part of Bachmann's bundle. The left panel shows the relationship between the coupling interval of premature impulses and refractory period (RP), conduction velocity (CV) and wavelength (WL). The prematurity zones A through D in the left panel correspond with the tracings in the right panel. Premature stimuli with a long coupling interval (zone A) elicited only single premature responses (A_2) after which sinus rhythm resumed. Moderately premature stimuli (zone B) were followed by a short series of Rapid Repetitive Responses. Still earlier coupled extrasystoles (zone C) sometimes resulted in a paroxysm of Atrial Flutter whereas premature stimuli given immediately after the refractory period frequently induced episodes of Atrial Fibrillation (panel D). These subsequent responses to increasingly premature impulses coincided with a gradual decrease in the values of both RP and CV and WL.

end of the refractory period (coupling interval <125 ms, panel D) frequently induced atrial fibrillation.

In the left panel, the zones A through D determine increasingly lower values of both refractory period and conduction velocity and wavelength. Thus the highest values of RP, CV and WL were associated with the absence of arrhythmias, while a decrease of the three parameters led to the occurrence of rapid repetitive responses; a further diminution allowed the

induction of atrial flutter, and atrial fibrillation occurred at the lowest values of RP, CV and WL. Because in this example the atrial response to progressively shorter coupled extrasystoles (from no arrhythmias to RRR, atrial flutter and finally atrial fibrillation) coincided with a decrease of the present values of both RP and CV and WL, at this point no inferences can be made as to which parameter correlates best with the occurrence of the different arrhythmias.

Correlation between wavelength and induction of arrhythmias.

We analyzed the atrial response (No Arrhythmias, Rapid Repetitive Responses, Atrial Flutter and Atrial Fibrillation) to a total of 149 early premature impulses with a relative prematurity (coupling interval minus the RP measured in the same experiment) of 0-50 ms.

Table 3.II gives the number of these various responses as observed with stimulation at four different atrial sites (right and left part Bachmann bundle, right and left atrial free wall). The overall frequencies of the different responses varied considerably. RRR were most frequently observed (38%), followed by AFib (24%) and No Arr (21%). AF1 (16%) was relatively seldom induced by early premature impulses. Table 3.II also shows that

Table 3.II Number of observed responses to premature impulses
elicited at four different atrial sites.

	<u>Dogs</u>	<u>No Arr</u>	<u>RRR</u>	<u>AF1</u>	<u>AFib</u>
BB Right	15	16 (43%)	19 (51%)	2 (6%)	-
BB Left	18	5 (10%)	13 (27%)	10 (21%)	20 (42%)
FW Right	15	8 (16%)	19 (39%)	10 (20%)	12 (25%)
FW Left	4	<u>3</u> (20%)	<u>6</u> (40%)	<u>2</u> (13%)	<u>4</u> (27%)
Total		32	57	24	36

BB Right = Right Part Bachmann Bundle
BB Left = Left Part Bachmann Bundle
FW Right = Right Atrial Free Wall
FW Left = Left Atrial Free Wall

there were striking differences in relative frequencies of induction of the various arrhythmias at the four atrial sites. At the site where the highest values of RP, CV and WL were measured (the right part of Bachmann's bundle), premature impulses almost always elicited no arrhythmias at all (43%) or just a run of RRR (51%). Only two episodes of AF1 were observed, whereas fibrillation was never induced at this site. At the left part of Bachmann's bundle (with the lowest values of RP, CV and WL) this relation was completely reversed. At this site AFib occurred most frequently (42%). AF1 (21%) and RRR (27%) were less often seen and in only 10% of cases the extrasystole was not followed by an arrhythmia. With stimulation of either the right or left atrial free wall, about 40% of premature beats caused episodes of AFib or AF1, another 40% elicited runs of RRR, whereas in 20% normal rhythm was not disturbed.

To find out how the different electrophysiological properties influenced the occurrence of arrhythmias, we correlated the values of refractory period, conduction velocity and wavelength as measured during control with the induction of the various arrhythmias. Figure 3.7 shows cumulative histograms of the occurrence of AFib (N=36), AF1 (N=24), RRR (N=57) and No Arr (N=32) in relation to the RP, CV and WL. The height of each bar gives the total number of observations in each class, while the relative number of the various responses is represented by the different shadings. Clearly, the three underlying electrophysiological properties all showed considerable overlap and no complete separation between the subpopulations was found. By means of discriminant analysis the optimal discriminating (critical) values of RP, CV and WL were determined and the predictive power of each variable for the four types of responses (AFib, AF1, RRR and No Arrhythmias) was calculated. In table 3.III the critical values of RP, CV and WL for the induction of arrhythmias are given together with the predictive power of these parameters. This analysis confirmed that these data do not justify any conclusions about the best correlation of any of the parameters with the occurrence of the different arrhythmias, the overall predictive value of the wavelength being only slightly higher (65%) than those of RP (59%) and CV (54%).

Figure 3.7: Cumulative histograms of the occurrence of No Arrhythmias (No Arr), Rapid Repetitive Responses (RRR), Atrial Flutter (AFI) and Atrial Fibrillation (AFib) in relation to the refractory period (RP), conduction velocity (CV) and wavelength (WL) of early premature impulses. The height of each bar indicates the total number of observations per class, whilst the different shadings represent the relative numbers of the four subpopulations. The induction of increasingly serious responses is associated with progressively lower values of both RP and CV and WL. Because all histograms show a comparable amount of overlap, the three measured electrophysiological parameters are about equally potent in discriminating between the different arrhythmias during control conditions.

Table 3.III Critical values and percentage correct classification of RP, CV and WL for the occurrence of different types of atrial response.

	<u>Refractory Period</u>		<u>Conduction Velocity</u>		<u>Wave- Length</u>	
	ms	%	cm/s	%	cm	%
AFib	88	61	86	72	7.5	83
AFI	95	41	97	50	9.3	55
RRR	103	58	112	35	11.7	53
No Arr		<u>74</u>		<u>69</u>		<u>75</u>
Overall correct classification		<u>59%</u>		<u>54%</u>		<u>65%</u>

3.3 Discussion

Spatial dispersion in refractory period.

On the basis of measurements of local refractory periods at 22 different sites in conscious dogs we found marked differences in local atrial refractoriness. In the drowsy state in which the dogs were tested (high natural vagal tone), there was a progressive shortening in refractory period along Bachmann's bundle from the right to the left appendage (figure 3.3). In the lower free wall of the right and left atrium only relatively small differences were found. During normal rhythm (panel A) the longest refractory period in the right atrium was 133 ms while in the left atrium the shortest RP was 107 ms. An early premature beat shortened local refractory periods by 29-37 ms and reduced the maximal difference in RP from 26 to 20 ms (panel B). Rapid pacing reduced refractoriness to a less extent (17-27 ms). The absolute degree of dispersion was hardly changed, the maximal difference in RP being 22 ms compared to 26 ms during a normal rhythm. These results differ in some aspects from the study by Han et al. (1966). Between six sites distributed over the right atrium they found a maximal difference of RP of 30 ms (pacing interval 350 ms), while in our group of dogs dispersion of refractoriness in the right atrium was only 11 ms. Furthermore,

they observed that shortening of the pacing interval from 600 to 350 ms resulted in a decrease of the spatial dispersion in refractoriness. However, a further shortening of the pacing interval did not affect the dispersion in refractory periods anymore, which is in agreement with our results. Also in clinical studies the degree of dispersion of atrial refractoriness was independent of heart rate (Luck et al. 1979, Michelucci et al. 1982).

Spatial dispersion in conduction velocity.

Compared to the spatial dispersion in refractory period, local differences in conduction velocity during slow pacing were less and varied from 123 cm/s in the free wall of the right atrium to 133 cm/s in the Bachmann bundle (table 3.I). Thus during a basic rhythm the observed spatial dispersion in wavelength was mainly determined by local differences in refractory period, variations in conduction velocity being of minor importance.

The observed small differences in basic conduction velocities became more marked during the propagation of premature beats and varied from 82 cm/s (Bachmann bundle from left to right) to 107 cm/s when the bundle of Bachmann conducted from right to left. The remarkable differences in conduction velocity along Bachmann's bundle when premature impulses were conducted either from left to right or from right to left may be caused by the observed systematic differences in local refractory periods along Bachmann's bundle. An early premature impulse starting at the right end of the Bachmann bundle will find progressively better recovered tissue ahead, whereas a premature impulse propagating in the opposite direction encounters myocardium with an increasing duration of the refractory period.

Spatial dispersion in wavelength.

As a consequence of the local differences in refractoriness and conduction velocity, also the wavelength varied from site to site. During normal rhythm the local wavelength differed from 14.5 cm (right part Bachmann bundle) to 17.7 cm (left part Bachmann bundle). During rapid pacing these values were 7.9 and 12.3 cm respectively, while an early premature beat showed spatial variations in wavelength from 6.6 to 10.7 cm (table 3.I). In all these situations the shortest wavelength was measured

in the left part of Bachmann's bundle. This area was also found to be the most favourable site to induce episodes of atrial tachy-arrhythmias (table 3.II). This is in agreement with the studies of Pastelin et al. (1978) who showed that rapid pacing at the left entrance of the interatrial bundle was an easy way to produce atrial flutter. They used this observation as an argument that the preferential internodal and interatrial pathways played an important role in providing a reentrant pathway for atrial flutter. However, the higher arrhythmogenic nature of the left part of the Bachmann bundle can also be explained on basis of the relatively short wavelength at that site together with the increasing refractory period from left to right. These local properties might highly favour the occurrence of unidirectional block and reentry in Bachmann's bundle. Ogawa et al. (1977) showed that premature impulses elicited at the high left atrium caused prolonged interatrial conduction, fragmentation of electrograms, longitudinal dissociation and reentry in the region of Bachmann's bundle. It is obvious that for a circuit to fit within such a relatively small part of the atria a short local wavelength is essential. In the present study the most striking distinction between the different areas of the atria was that the left part of Bachmann's bundle both was a preferential pacing site for the induction of atrial fibrillation and exhibited the shortest wavelength.

Anisotropy in the healthy, intact canine atrium.

In the past years it has become clear that both atrial and ventricular myocardium possess anisotropic properties (Draper et al. 1959, Sano et al. 1959, Clerc 1976). The excellent studies of Spach et al. (1979, 1981, 1982, 1986) have provided direct evidence that impulse conduction proceeds faster along the long axis of a bundle of parallel cardiac fibers than in the transverse direction. In isolated atrial bundles of the dog they found longitudinal conduction varying between 1.0-1.3 m/s and transverse conduction varying between 0.04-0.12 m/s (Spach et al. 1982). In pieces of human myocardium excised from the right atrial appendage corresponding values of 0.50 m/s and 0.11 m/s in young subjects and 0.69 and 0.07 m/s in elderly patients were reported (Spach et al. 1986). In our studies we measured the conduction velocity in conscious dogs both along Bachmann's bundle (longitudinal propagation) and in the right and left atrial free wall parallel to the AV ring. In these latter areas it is difficult to

indicate an overall fiber direction. At the endocardial side a number of large bundles is found, which run perpendicular to the AV-ring. Under these bundles there is a layer of numerous small interconnecting muscle bundles which are oriented in all possible directions and form an intertwining network. These smaller bundles also interconnect the larger ones (Goodman et al. 1971). Most epicardially, a thin muscle layer exists in which, macroscopically, no individual bundles can be identified. During regular pacing the conduction velocity as measured over a distance of 6 cm along Bachmann's bundle was 1.27-1.33 compared to 1.23-1.32 m/s along the AV ring (measuring distance 4 cm). In other words, despite the big differences in structure, we did not find significant differences in conduction velocity between Bachmann's bundle and the inferior free wall of the atria. During an early premature beat, differences in local conduction velocity varied from 107 cm/s in the right part of Bachmann's bundle to 83 cm/s in the right atrial free wall, but also in this situation we did not measure the low values reported by Spach et al. (1982, 1986). A possible explanation for this discrepancy may be found in the different distances over which conduction velocities were measured, which amounted to 4-6 cm in our measurements and from 200 μ m to 1.5 mm in their experiments (Spach et al. 1982, 1986). Small areas of slow conduction caused by anisotropic propagation will not seriously delay the propagation of a wide depolarization front over a longer distance, because they are bypassed by fast conducting routes. Therefore we would like to take Spach's conclusion that, due to age related progressive electrical uncoupling of side-to-side connections between atrial fibers, micro-reentry may occur in areas of 1-2 mm² with some precaution (Spach et al. 1986). The conduction velocity reported in that study was 0.07 m/s. When the refractory period is estimated at 150 ms, we can calculate the wavelength to be $\pm$ 1 cm. Thus, calculation of a WL of 1 cm based on a CV of 0.07 m/s implicates that, for a reentrant circuit of that size to exist, conduction must be that slow over a continuous route of 1 cm. This is an extrapolation of 50 times the distance over which the actual CV was measured (200 μ m). Our observations indicate that such an extrapolation is hazardous. In healthy atrial myocardium large areas of slow conduction were not encountered. However, in diseased atria with progressive fibrotic changes and abnormal electrophysiological characteristics, larger continuous areas of poorly coupled fibers may arise (Ten Eick

et al. 1979, Boyden et al. 1984). The frequent occurrence of atrial fibrillation in those hearts may be related to the presence of larger areas of impaired conduction where the wavelength is short relative to the available tissue mass.

Atrial electrophysiology and the occurrence of arrhythmias.

Both from experimental and clinical studies it is known that one critically timed stimulus can induce atrial arrhythmias. In some papers the role of slow conduction of the extrasystole is stressed (Leier et al. 1978, Plumb et al. 1981, Cosio et al. 1983, Buxton et al. 1984). Other authors point out that a short refractory period is an important factor in the arrhythmogenic mechanism (Andrus and Carter 1930, Wyndham et al. 1977, Engel et al. 1978, Luck et al. 1979, Michelucci et al. 1982). However, both on theoretical and experimental grounds the combination of refractory period and conduction velocity as expressed in the wavelength is of prime importance in the occurrence of reentrant arrhythmias (Mines 1913, Lewis 1925, Allesie et al. 1977, Smeets 1983, Wellens et al. 1984). We measured the effects of variations of rate and rhythm on the refractory period, conduction velocity and wavelength in the atria of 19 chronically instrumented conscious dogs, and correlated changes in these parameters to the inducibility of atrial arrhythmias.

The normal length of the atrial excitation wave of 14-18 cm as measured during a regular rhythm offers a highly effective protection against the possibility that the impulse is trapped in a circuitous pathway. To start such a circuit, an unidirectional conduction block of at least 7-9 cm would be required. The occurrence of such a large area of conduction block is rather unlikely. In addition, the dimensions of the normal atria can hardly accommodate a circuit of that size. It is one of the basic electrophysiological properties of cardiac tissue that the duration of the refractory period shortens with increasing heart rate. This adaptation to higher heart rates is appropriate to guarantee that the cardiac fibers restore their excitability during a shorter diastole. On the other hand, the shortening of the refractory period together with the decreased conduction velocity at rapid heart rates reduces the wavelength by 30-45% and thus decreases the degree of safety against reentrant arrhythmias. Furthermore, once established, the very rapid rate of a reentrant tachycardia will shorten the

wavelength even further, thereby attributing to the perpetuation of the arrhythmia or even causing atrial fibrillation. The degeneration into atrial fibrillation, as can occur during overdrive pacing of atrial flutter (Wellens 1971) or, spontaneously, during a paroxysm of supraventricular tachycardia (Lewis 1910, Sung et al. 1977, Roark et al. 1986), could be explained by a marked reduction of the wavelength at these high heart rates. The results of Attuel et al. (1982) are interesting in this respect. They found that patients who did not exhibit a rate dependent shortening of atrial refractoriness, showed an increased vulnerability to atrial tachyarrhythmias. These patients had already during slow rhythms the short refractory periods which normal subjects attained only at rapid heart rates. The short RP and consequently short wavelength, present also at slow, normal heart rates, can explain their predisposition to atrial arrhythmias.

Like a rapid heart rate, also premature beats cause changes in electrophysiological properties which result in shortening of the wavelength. This reduction of the wavelength, based on both a decrease of the refractory period and conduction velocity, became apparent at coupling intervals shorter than 250 ms and progressed with higher degrees of prematurity. This gradual shortening of the wavelength with increasing prematurity was accompanied by the induction of increasingly serious arrhythmias. At a wavelength shorter than 11.7 cm short bursts of rapid repetitive activity were observed. At still shorter wavelengths (<9.3 cm) episodes of flutter occurred, whereas very early premature beats with a wavelength of less than 7.5 cm frequently induced atrial fibrillation. With a wavelength of 7.5 cm a line of conduction block of only 3-4 cm is required for the initiation of intra-atrial reentry. Obviously, the required inhomogeneity for such small conduction blocks is naturally present in normal canine atria. The diameter of the resulting circuits can be estimated to be as small as 2.4 cm (WL/π) and the surface area 4.5 cm² ($WL^2/4\pi$). Compared to the dimensions of the canine atria (35 cm² on an average in our studies), about 7-8 circuits of this size could be simultaneously present in the atrial myocardium.

On the basis of results presented in this chapter it is not possible to conclude which of the three measured variables (RP, CV and WL) is the best parameter for the susceptibility to atrial arrhythmias. The successive occurrence of rapid repetitive responses, atrial flutter and atrial fibril-

lation coincided with a gradual decrease of both RP and CV and WL. Also the predictive power of the three parameters for the different arrhythmias did not differ much, the predictive values of RP, CV and WL being respectively 59%, 54% and 65%.

In the following chapters, we will study the effects of pharmacological manipulation of RP, CV and WL and the related occurrence of tachy-arrhythmias. Although refractoriness and conduction velocity are intrinsically related, cardiac drugs may affect RP and CV in a quantitatively different way. In this way we will attempt to unmask the individual significance of RP, CV and WL for the occurrence of atrial tachy-arrhythmias.

CHAPTER IV

THE INFLUENCE OF THE AUTONOMIC NERVOUS SYSTEM ON THE ELECTROPHYSIOLOGICAL PROPERTIES OF THE ATRIA

Variations in autonomic nervous activity are known to affect the electrophysiological properties of the atria and to change the susceptibility to atrial tachy-arrhythmias. The effects of the administration of autonomic transmitters or stimulation of cardiac nerve endings have been studied both in isolated preparations and in anaesthetized animals. Early observations on the relation between vagal activity and atrial rhythm were already made at the end of the last century (MacWilliam 1887, Fischel 1897, Knoll 1897) and after some dispute it was unequivocally established that in such models high vagal activity was associated with short atrial refractory periods and a strong proneness to tachy-arrhythmias. For a long time, controversy centered around whether these arrhythmias were automatic or reentrant in nature. More recent reports strongly suggest that intra-atrial reentry is highly favoured by vagal activity because of shortening of atrial refractoriness (Allessie et al. 1977, 1984, 1985, Smeets et al. 1986). Increased sympathomimetic activity has less clear-cut effects on atrial electrophysiology, with both shortened (Brooks et al. 1955, Farges et al. 1977), prolonged (Smeets et al. 1986) and unchanged (Hoffman and Cranefield 1960, Vargas et al. 1975) refractoriness reported. Conduction velocity is reported to be either not changed or slightly increased by both sympathetic and parasympathetic activity (Childers et al. 1968, Smeets et al. 1986). In human beings, spontaneous fluctuations in vagal tone can also affect the occurrence of atrial flutter and fibrillation (Coumel et al. 1983).

In this chapter we investigated the effects of both naturally occurring changes in autonomic tone and the administration of autonomic mimetic and blocking agents on refractory period, conduction velocity and length of the atrial excitation wave. Changes in these electrophysiological parameters were correlated with the inducibility of atrial arrhythmias.

Because dispersion of refractoriness is thought to be another important

factor in the initiation of reentrant arrhythmias, we also studied how this dispersion is influenced by modulations of autonomic tone.

4.1 Experimental protocol

The wavelength was measured in the right and left part of the Bachmann bundle and the free wall of either the right or left atrium. The basic pacing interval was 350 ms except during acetylcholine, atropine and isoproterenol administration, during which a basic cycle length of 270-300 ms was needed to overpace the accelerated sinus rhythm.

The effects of acetylcholine (Dispersa AG) were studied during a continuous infusion of 0.02 mg/kg/min. Atropine (ACF Chemiefarma) was administered in a single dosage of 0.2 mg/kg injected over a 5 minutes' period. The sympathomimetic agent isoproterenol (Dispersa AG) was infused at a rate of 0.5 µg/kg/min and the betablocking agent propranolol (ICI Farma) was given in a dosage of 0.3 mg/kg (given over 5 minutes). Measurements of the effects of acetylcholine and isoproterenol were begun 2 minutes after the start of the infusion, and of atropine and propranolol 15 minutes after the injection. All drugs were administered through a catheter in the left atrium. In addition, the effects of a change in autonomic tone was studied by exercising the dogs on a treadmill (5 km/hr).

The number of dogs in which the different interventions were tested is given in table 4.I. Results were obtained at four different atrial sites: the right and left part of the Bachmann bundle, and the right and left atrial free wall. The reason that the number of observations can differ for the various sites, is that not all measuring sites could be used in each dog because of high stimulation thresholds or poor quality of recorded electrograms. Furthermore, in three dogs an electrode was implanted on the left instead of the right atrial free wall and in one dog on either atrial free wall.

Dispersion of atrial refractoriness was studied by measuring the refractory period at 22 different sites distributed over Bachmann's bundle (13 dogs) and the right (N=10) and left (N=4) atrial free wall.

4.2 Results

Autonomic influence on the length of the atrial excitation wave.

In the left panel of figure 4.1 the effects of acetylcholine (N=18) and atropine (N=11) on the refractory period, conduction velocity and wavelength of extrasystoles with varying prematurity are plotted. Results obtained in the left part of Bachmann's bundle are given. The control curve is represented by the interrupted line. Administration of acetylcholine substantially reduced the refractory period by 30% at long coupling intervals and 20% at early prematurity. Conduction velocity was not affected but the curve is shifted to the left because the shortest possible coupling interval has decreased. Consequently, acetylcholine shortened the wavelength from 14.5 to 10.2 cm (-30%) during normal pacing and from 6.6 to 5.3 cm (-20%) at early premature beats. The administration of atropine had an opposite effect. The refractory period was increased by 13-18%. Conduction velocity was not changed but now the curve is moved to the right because of an increase of the shortest possible A1-A2 interval. Thus, vagal blockade by atropine increased the wavelength of a regular impulse to 16.5 cm (+14%) and of the earliest premature beat to 7.7 cm (+17%). Slackening of vagal tone by treadmill exercise had a similar effect. Atrial refractoriness prolonged with 4-11% while conduction velocity was essentially unchanged. As a result the WL of early premature beats increased from 6.6 cm to 7.3 cm (+11%).

The effects of the administration of isoproterenol (N=5) and propranolol (N=6) are shown in the right panel of figure 4.1. It is clear that in contrast to the important effects of parasympathetic activity, variations in sympathetic tone had virtually no consequence on refractoriness, conduction velocity or wavelength. The effects of modulation of the autonomic activity by various interventions on the RP, CV and WL at four atrial sites are summarized in table 4.1.

Figure 4.1: Autonomic influence on atrial electrophysiological properties. Control values are represented by the interrupted line. The left panel shows the effects of acetylcholine and atropine on the refractory period (RP), conduction velocity (CV) and wavelength (WL) of extrasystoles with varying prematurity, as measured in the left part of Bachmann's bundle. The administration of acetylcholine (●, N=18) resulted in a 20-30% shortening of the wavelength, due to a reduction of RP without affecting CV. Vagal blockade by atropine (▼, N=11) had a qualitatively opposite effect and increased the wavelength by 15% because of a prolongation of RP. In the right panel the effects of isoproterenol (■, N=5) and propranolol (★, N=6) are shown. It is clear that both sympathomimetic and sympatholytic activity exerted little effect on RP, CV and WL in the atrium.

Table 4.1 The effects of modulation of the autonomic nervous sytem on Refractory Period (RP), Conduction Velocity (CV) and Wave-length (WL) at four different atrial sites.

<u>BB Right</u>		<u>Regular Rhythm</u>			<u>Earliest Premature Beat</u>		
	N	RP (ms)	CV (cm/s)	WL (cm)	RP (ms)	CV (cm/s)	WL (cm)
Control	15	133 _± 7	133 _± 12	17.7 _± 1.7	99 _± 7	107 _± 13	10.7 _± 1.7
Acetyl- choline	11	86 _± 13 ^{***}	137 _± 10	11.8 _± 2.3 ^{***}	66 _± 10 ^{***}	106 _± 11	7.0 _± 1.4 ^{***}
Atropine	10	149 _± 4 ^{***}	130 _± 5	19.4 _± 0.8 [*]	113 _± 4 ^{***}	114 _± 12	12.8 _± 1.3 ^{**}
Treadmill	7	145 _± 5 ^{**}	131 _± 5	19.1 _± 0.7	104 _± 4	110 _± 12	11.5 _± 1.2
Isopro- terenol	5	120 _± 3 ^{**}	135 _± 9	16.2 _± 1.4 [*]	89 _± 7 [*]	110 _± 10	9.9 _± 1.5
Propra- nolol	6	134 _± 6	133 _± 10	17.8 _± 1.4	102 _± 5	104 _± 11	10.6 _± 1.2
<u>BB Left</u>							
Control	18	114 _± 7	127 _± 10	14.5 _± 1.7	80 _± 7	82 _± 6	6.6 _± 0.5
Acetyl- choline	18	80 _± 11 ^{***}	127 _± 12	10.2 _± 1.8 ^{***}	63 _± 11 ^{***}	83 _± 16	5.3 _± 1.1 ^{***}
Atropine	11	129 _± 11 ^{***}	127 _± 4	16.5 _± 1.5 ^{**}	94 _± 10 ^{***}	82 _± 6	7.7 _± 1.1 ^{***}
Treadmill	8	119 _± 12	129 _± 4	15.2 _± 1.3	89 _± 7 ^{***}	82 _± 5	7.3 _± 0.9 [*]
Isopro- terenol	5	110 _± 10	130 _± 8	14.3 _± 1.0	75 _± 7	84 _± 8	6.3 _± 1.0
Propra- nolol	6	113 _± 8	128 _± 12	14.5 _± 1.4	82 _± 3	80 _± 6	6.6 _± 0.6

BB Right = Right Part Bachmann Bundle
BB Left = Left Part Bachmann Bundle

*** = p<0.001
** = p<0.01
* = p<0.05

Table 4.1 continued.

FW Right		Regular Rhythm			Earliest Premature Beat		
	N	RP (ms)	CV (cm/s)	WL (cm)	RP (ms)	CV (cm/s)	WL (cm)
Control	15	124 _± 9	123 _± 13	15.2 _± 1.5	92 _± 7	83 _± 8	7.6 _± 1.0
Acetyl- choline	11	*** 81 _± 13	123 _± 12	*** 10.1 _± 2.2	*** 64 _± 9	81 _± 8	*** 5.1 _± 0.8
Atropine	7	*** 154 _± 4	118 _± 12	** 18.1 _± 2.1	*** 108 _± 6	90 _± 11	*** 9.8 _± 1.2
Treadmill	7	** 142 _± 12	124 _± 9	** 17.7 _± 2.3	* 100 _± 8	87 _± 10	* 8.7 _± 1.0
Isopro- terenol	5	* 116 _± 5	125 _± 6	14.5 _± 1.2	* 85 _± 8	86 _± 7	7.3 _± 1.2
Propra- nolol	5	121 _± 7	125 _± 8	15.1 _± 1.1	90 _± 6	82 _± 5	7.4 _± 1.0
FW Left							
Control	4	111 _± 7	132 _± 9	14.7 _± 1.9	81 _± 6	95 _± 7	7.7 _± 0.7
Acetyl- choline	4	*** 67 _± 8	131 _± 7	** 8.7 _± 1.1	** 54 _± 4	* 115 _± 9	6.3 _± 0.9
Atropine	4	122 _± 8	129 _± 3	15.7 _± 1.4	91 _± 9	104 _± 9	* 9.5 _± 1.3
Treadmill	4	120 _± 14	132 _± 3	15.9 _± 2.1	87 _± 7	100 _± 10	8.7 _± 1.5
Isopro- terenol	4	106 _± 6	133 _± 8	14.1 _± 0.9	78 _± 10	100 _± 6	7.8 _± 1.0
Propra- nolol	4	114 _± 8	134 _± 10	15.3 _± 1.7	82 _± 8	95 _± 7	7.8 _± 1.0

FW Right = Right Atrial Free Wall
FW Left = Left Atrial Free Wall

*** = p<0.001
** = p<0.01
* = p<0.05

Parasympathetic influence on the rate of atrial tachy-arrhythmias.

The left panel of figure 4.2 shows an example of the effect of a short infusion of acetylcholine on the interval of an episode of atrial flutter. A gradual and transient shortening of the cycle length from 95 to 70 ms was observed immediately following the infusion. Longer lasting infusions of acetylcholine invariably led to degeneration of flutter into fibrillation.

FLUTTER INTERVAL

Figure 4.2: The effects of acetylcholine (left panel) and atropine (right panel) on the beat to beat interval of atrial flutter. A shortlasting infusion of the parasympathetic agent caused a gradual and transient decrease of the flutter interval from +96 to 70 ms. Parasympathetic blockade by atropine had an opposite effect. The interval of another period of atrial flutter was increased from +88 to 98 ms. These findings support the concept that in our studies atrial flutter is based on functional reentry (see text).

The right panel shows the effect of vagal blockade by atropine on the interval of another case of atrial flutter. The injection of atropine was followed by a gradual increase of the flutter interval from +87 ms to 98 ms. Furthermore, the respiration coupled fluctuations of the flutter cycle length were abolished. Since atropine is a long-acting drug, these effects were not readily reversed. Besides a slowing of the flutter rate we also frequently observed a termination of atrial tachy-arrhythmias by atropine.

Figure 4.3 shows local recordings of atrial fibrillation during control (upper tracing) and during the administration of acetylcholine (lower tracing). The intervals between the successive activations are given below the tracings. In both situations the recordings show the characteristics of fibrillation: varying amplitude and configuration of electrograms and

LOCAL RECORDINGS OF ATRIAL FIBRILLATION

Figure 4.3: Local recordings of atrial fibrillation during control (panel A) and during the administration of acetylcholine (panel B). The intervals (in milliseconds) between successive activations are given below the tracings. V denotes ventricular complex. In both situations, the varying shape and amplitude of electrograms and the irregularity of activation interval, which are characteristic of fibrillation, are easily visible. However, the activation intervals were clearly shorter during acetylcholine, resulting in a higher fibrillation rate. During control and acetylcholine administration mean fibrillation rate (N=4 dogs) was 833 and 1154 "beats" per minute, respectively.

irregularity of activation intervals. However the average length of the activation intervals was clearly shorter during acetylcholine. We determined the rate of longer periods of fibrillation before and during the administration of acetylcholine in four dogs. The parasympathetic agent markedly increased the atrial fibrillation rate from 833±81 to 1154±219 "beats" per minute.

Autonomic influence on spatial dispersion of refractoriness.

Local dispersion of refractory periods in the atrium is influenced by changes in autonomic activity (Alessi et al. 1958, Ninomyia 1966, Zipes et al. 1974). These studies were carried out in anaesthetized open-thorax dogs and vagal tone was varied by artificial electrical stimulation of the cut

end of the vagal trunk. To investigate the influence of modulations in autonomic tone on dispersion in normal conscious dogs, we measured the RP of a regular rhythm (300 ms interval) at 22 different sites located at the free wall of the right and left atrium and along the bundle of Bachmann during complete autonomic blockade (atropine + propranolol), treadmill exercise, during a physiologically high vagal tone (drowsy dogs) and during the administration of acetylcholine. The mean local values and related histograms are given in figure 4.4. In the absence of autonomic influences (panel A) there were marked differences in the refractory period between different parts of the atria. This intrinsic spatial dispersion was only slight in the free wall of the right atrium, the difference between the shortest and longest refractory period being no more than 6 ms (156-162 ms). However, along the bundle of Bachmann significant differences in refractoriness were measured. In all dogs a consistent shortening of the local refractory period was found from the right (155 ms) to the left appendage (125 ms). The free wall of the left atrium again showed uniform refractoriness (from 117 to 124 ms). This systematic transition in duration of refractoriness resulted in a maximal difference in refractory period of 45 ms between the right and the left atrium. Also in the three other situations (panel B, C and D) the same pattern of refractory period distribution was found (small differences in both the right and left atrial wall, but a gradual shortening of RP from the right to the left auricle). However, both the duration of the RP and the degree of dispersion varied considerably. During treadmill exercise (panel B) the maximal difference in RP between the right and left atrium decreased to 26 ms (119-145 ms). During a high vagal tone (panel C) the maximal difference was 26 ms (107-133 ms). Administration of acetylcholine (panel D) resulted in a strong overall decrease in refractory period, the greatest difference between the right and the left atrium being 33 ms (60-93 ms). This decrease in spatial dispersion in refractory periods by parasympathetic activity was caused by the fact that the RP in areas with a long intrinsic refractory period (right atrium) was reduced more markedly than in areas with a shorter intrinsic refractory period (left atrium). This is clearly reflected by the histograms at the right part of figure 4.4. Increasing vagal activity or administration of acetylcholine shifts the histograms to the left and narrows their range.

A ATROPINE + PROPRANOLOL

B TREADMILL EXERCISE

C HIGH VAGAL TONE

D ACETYLCHOLINE

In table 4.II the sites are tabulated in order of duration of RP during complete autonomic blockade. Numbers 1-7 were measured at the right atrial free wall, numbers 8-11 at the right and numbers 12-15 at the left part of Bachmann's bundle, while numbers 16-22 were found at the left atrial free wall. The absolute and relative degree of RP shortening by a physiologically high vagal activity and by the administration of acetylcholine are shown. It is clear that a high vagal activity decreases the intrinsic RP strongly in the right atrial free wall (20-24%), markedly less in Bachmann's bundle (11-15%), while the free wall of the left atrium experiences the least effect with a RP shortening of 4-11%. In contrast, the effect of direct administration of acetylcholine does not vary in different parts of the atria, the refractory period now being strongly and uniformly shortened by 41-50%.

As a consequence of the locally different actions of a physiologically high vagal activity on refractoriness, also the wavelength was nonuniformly shortened. Compared to the atropinized state, the wavelength of a regular rhythm in a drowsy state decreased by 16% in the right atrial free wall, 9 and 12 % respectively in the right and left part of Bachmann's bundle, and 6% in the free wall of the left atrium. However administration of acetylcholine shortened the wavelength homogeneously by 38-44% (table 4.I).

Figure 4.4: Dispersion of refractoriness in the atrium during different states of autonomic control as measured along Bachmann's bundle (N=13 dogs) and in the free wall of the right (N=10) and left (N=4) atrium. The numbers in the maps indicate the mean refractory period (RP) at that site during a regular rhythm (300 ms interval). Next to the maps the related histograms of the distribution of local RP are given. In all situations there were only slight differences in RP in the free wall of both the right and the left atrium, whilst a marked shortening of RP along Bachmann's bundle from right to left was found. During complete autonomic blockade (panel A) the maximal difference in RP between the right and left atrium was highest (162-117 ms). During treadmill exercise (panel B) RP was shorter and maximal dispersion less (145-119 ms). In a high vagal state RP was further shortened at all sites and the dispersion reduced to 26 ms (133-107 ms), as indicated by the leftward shift and narrowing of the histogram. Administration of acetylcholine (panel D) caused a strong overall decrease in RP with a dispersion of 33 ms (60-93 ms).

Table 4.II The influence of a physiologically high vagal tone and the administration of acetylcholine on the intrinsic Refractory Period (RP) at 22 atrial sites.

		<u>Autonomic blockade</u>	<u>High vagal tone</u>		<u>Acetylcholine</u>			
		RP (ms)	RP (ms)	d (ms)	d (%)	RP (ms)	d (ms)	d (%)
Right Atrial Free Wall	1	162	123	-39	-24	93	-69	-43
	2	161	128	-33	-20	83	-78	-48
	3	161	127	-34	-21	82	-79	-49
	4	160	122	-38	-24	87	-73	-46
	5	160	122	-38	-24	83	-77	-48
	6	159	124	-35	-22	82	-77	-48
	7	156	124	-32	-21	81	-75	-48
Right Part B.B.	8	155	132	-23	-15	84	-71	-46
	9	152	130	-22	-14	80	-72	-47
	10	149	133	-16	-11	86	-63	-42
	11	142	125	-17	-12	74	-68	-48
Left Part B.B.	12	136	118	-18	-13	73	-63	-46
	13	129	114	-15	-12	76	-53	-41
	14	127	112	-15	-12	72	-55	-43
	15	125	107	-18	-14	70	-55	-44
Left Atrial Free Wall	16	124	119	-5	-4			
	17	124	115	-9	-7	66	-58	-47
	18	124	110	-14	-11			
	19	123	112	-11	-9	65	-58	-47
	20	119	109	-10	-8	60	-59	-50
	21	118	111	-7	-6	67	-51	-43
	22	117	111	-6	-5			

B.B. = Bachmann Bundle

4.3 Discussion

Autonomic tone and atrial reentrant arrhythmias.

In our experiments variations of the vagal state of the dogs clearly affected atrial electrophysiological parameters and the induction of atrial arrhythmias. The administration of the vagomimetic agent acetylcholine shortened the wavelength in the atrium by decreasing the refractory period without affecting conduction velocity. This is in agreement with the well-

known arrhythmogenic effect of vagal stimulation. In the presence of a short wavelength even small patches of local conduction block will suffice to set up one or more reentrant circuits. Apparently such areas of conduction block are abundantly present in the normal canine atrium because during acetylcholine administration early premature impulses almost always caused atrial fibrillation (see table 6.I). Furthermore, a short wavelength contributes to the perpetuation of the fibrillatory process because it favours the existence of many reentering impulses in the given tissue mass, thus diminishing the chance of simultaneous extinction of the multiple wandering activation waves. When the wavelength is taken as the perimeter of intra-atrial circuits, the surface area of a circuit is given by $WL^2/4\pi$. With an estimated total atrial surface area of 35 cm^2 (which was the average atrial surface area in our study), a wavelength of 6 cm during acetylcholine administration would allow the simultaneous existence of about 12 wavelets. This number is amply higher than the minimal number of wavelets (6) required for stable atrial fibrillation (Allessie et al. 1985).

Slackening or inhibition of vagal activity by exercise or atropine administration prolonged the length of the excitation wave by an increase of atrial refractoriness. In the absence of vagal activity the atrial wavelength of premature impulses measured about 9.5 cm and, using the same formula as above, it can be calculated that this WL would permit only 5 wavefronts to wander simultaneously through the atria, which is at the lower limit of the number necessary for stable atrial fibrillation. This is in agreement with our observation that atropine and treadmill activity often interrupted periods of atrial fibrillation or prevented its induction.

The observed shortening of the cycle length of pre-existent atrial flutter by a short infusion of acetylcholine (figure 4.2) indicates that in our studies such an arrhythmia is due to intramyocardial reentry of the leading circle type (Allessie et al. 1977). In this type of reentry without an anatomical obstacle there is no excitable gap in the circuit and the revolution time is totally determined by the refractory period. Therefore a shortening of the refractory period by acetylcholine will immediately decrease both the circuit size and the revolution time. In case of reentry around an anatomical obstacle shortening of the refractory period will not influence the cycle length, since in this type of reentry the revolution

time is determined by the conduction velocity of the circulating impulse and the size of the obstacle. Only when the circuit contains partially recovered tissue, a decrease of the RP will shorten the cycle length because such an area will also become fully excitable and thus will conduct the circulating impulse at a higher speed (Frame et al. 1986). Lengthening of the refractory period on the other hand will initially increase the cycle length, as we observed after the administration of atropine. If the RP is further lengthened without a change in the conduction velocity, the accompanying increase of the wavelength will increase the size of the intra-atrial circuit, and when the circuit size outgrows the size of the atria the flutter will be interrupted.

Boyden (1986) also observed a decrease of atrial flutter cycle length by a parasympathomimetic agent (metacholine) in conscious dogs with right atrial enlargement. However, in her studies vagal blockade by atropine did not influence the flutter rate. Also the administration of a pressor dose of phenylephrine (which was used to cause reflex vagal activity) did not significantly decrease the flutter interval, although AV nodal block occurred. This might indicate that in the enlarged right atrium vagal activity has decreased.

Also in humans the relationship between vagal tone and atrial arrhythmias has been described: Holter-monitoring in patients showed that paroxysms of fibrillation or flutter started during periods of relative sinus bradycardia (Coumel et al. 1983). The observation of Goel and Han (1970) that bradycardia associated atrial arrhythmias are abolished by a spontaneous or atropine induced acceleration of sinus rate might also be explained by a diminished vagal tone and consequently a prolonged wavelength.

The observed increase of the atrial fibrillation rate during acetylcholine administration (figure 4.3) has been described previously by Rosenblueth (1953) and Farges et al. (1978). In our opinion it supports the concept that atrial fibrillation is based on multiple wandering, intramyocardial circuits. Both the shortening of the refractory period and the higher number of reentering wavelets resulting from a shorter wavelength, will lead to an increased local activation rate.

Both adrenergic stimulation (isoproterenol administration) and beta-blockade (propranolol administration) failed to have significant effects on

the atrial wavelength and did not affect the inducibility of arrhythmias. In the human heart however, also "adrenergic fibrillation" is recognized and beta-blocking agents can be effective in its treatment (Coumel et al. 1983). If our measurements may be extrapolated to humans, this cannot be explained by changes in the wavelength of the atrial impulse. Another explanation might be that diseased atria are more sensitive to adrenergic agents which, by giving rise to increased ectopic activity (Boyden et al. 1984), can cause atrial arrhythmias by itself or favour the chance on the induction of reentry by increasing the number of atrial premature beats.

Spatial dispersion in refractoriness.

On the basis of measurements of local refractory periods at 22 different sites in conscious dogs both during absence and presence of vagal activity as well as during administration of acetylcholine, we found marked differences in local atrial refractoriness. Under all circumstances there was a progressive shortening in refractory period along Bachmann's bundle from the right to the left appendage (figure 4.4). In the lower free wall of the right and left atrium only relatively small differences were found. In the absence of vagal activity either by atropine or treadmill exercise, the differences in refractoriness between the right (162 ms) and the left (117 ms) atrium were highest. During control with the dogs half asleep, atrial refractoriness was shortened and local differences were diminished. Under these circumstances the longest refractory period in the right atrium was 133 ms while in the left atrium the shortest RP was 107 ms. The decreased spatial dispersion in atrial refractory periods by vagal activity is caused by a relatively stronger shortening of RP at sites with a long intrinsic refractory period (20-24%, right atrium) compared to a shortening of 4-11% in the left atrium. In contrast to increased vagal activity, direct administration of acetylcholine resulted in a uniform shortening of the refractory period by 41-50%. This indicates that the higher degree of RP shortening in the right atrium during a high vagal tone is not due to a higher sensitivity to acetylcholine but either to a higher tone of the right vagal trunk or to a more dense vagal innervation of the right atrium. These data are partly in accordance with the results of Zipes et al. (1974). In anaesthetized dogs with cut vagi these authors reported that the RP was longer in the right than in the left atrium. They also found that vagal

stimulation had a stronger effect on the refractory period in the right atrium. In contrast to our studies however, vagal stimulation shortened the RP in the right atrium to such extent that the spatial dispersion in refractory periods was increased. An increase in local differences in RP by vagal stimulation was also reported by Alessi et al. (1958). In our studies in chronically instrumented conscious dogs with physiological vagal activity we found that increased vagal tone decreased the intrinsic spatial dispersion of atrial refractory periods. This difference might be explained by the fact that electrical stimulation of cut vagi in an anaesthetized dog gives a much higher release of autonomic transmitters than ever occurs under physiological circumstances.

The actual decrease in spatial dispersion of refractoriness during physiological vagal activity means that it plays no role in the initiation of vagally induced atrial fibrillation. The increased vulnerability to atrial fibrillation by vagal activity is solely caused by shortening of the wavelength of the atrial impulse.

CHAPTER V

THE EFFECTS OF OUABAIN, LIDOCAINE, QUINIDINE, PROPAFENONE AND D-SOTALOL ON WAVELENGTH AND ATRIAL ARRHYTHMIAS

In the past many different models have been used to test the anti-arrhythmic efficacy of cardiac drugs. The actions of these compounds on certain aspects of cellular electrophysiology or on experimentally induced arrhythmias in the isolated or in situ heart were considered to be predictive for their usefulness in treating clinical arrhythmias. However, the problem remained that the exact mechanisms underlying various cardiac arrhythmias were not always completely understood and consequently it was uncertain which electrophysiological properties are relevant in preventing or interrupting these arrhythmias. Tests which are based on the causal mechanism of arrhythmias are more likely to yield satisfactory results. Since atrial arrhythmias as rapid repetitive activity, atrial flutter and atrial fibrillation are thought to be based on intramyocardial reentry, we hypothesized that the action of cardiac drugs on the length of the excitation wave should be of primary importance to predict their efficacy against these arrhythmias. In this chapter we describe the effects of propafenone, lidocaine, quinidine, d-sotalol and ouabain on the length of the atrial impulse, both during slow and rapid pacing and during premature beats.

5.1 Experimental Protocol

A total of nineteen dogs of both sexes weighing between 30 and 40 kilograms were used for this study. The following drugs were administered through a catheter in the left atrium.

Propafenone (Rytmonorm, Knoll) was administered in a dosage of 4 mg/kg over a 2 minutes' period. Measurements were started 20 minutes after administration. The decay in plasma concentrations has been reported to be

relatively slow after this interval (Karagueuzian et al. 1982, Li et al. 1986).

Lidocaine (Xylocaine, Astra) was given in a bolus injection of 100 mg over a period of 1 minute, which was followed by a continuous infusion at the rate of 0.6 mg/kg/min. Measurements were begun 30 minutes after the bolus injection.

Quinidine sulfate (ACF Chemiefarma) was tested at a dosage of 10 mg/kg which was injected over a 10 minutes' period. The effects were studied 30 minutes after injection of the drug.

The experimental drug d-sotalol (Bristol-Myers Company) was administered at a dosage of 8 mg/kg injected over 5 minutes. Testing of its effects was started 45 minutes after the administration. Blood levels of d-sotalol have been reported to be relatively constant after this interval, with a plasma half-life of 3.7 hours (Kato et al. 1986).

Ouabain (ACF Chemiefarma) was given in a continuous infusion of 0.036 μ g/kg/min after a bolus injection of 20 μ g/kg, a regime which results in rather constant plasma concentrations (Rhee et al. 1976). The experiment was started 30 minutes after the bolus injection.

Stimulation threshold determination was repeated at the start of each experiment. Because a slow change in plasma concentrations of the tested drugs might cause hysteresis, results obtained at the start and at the end of the experiments were always compared, but no systematic differences were found. Changes in parameters induced by the various drugs were statistically analysed by the unpaired Student's t-test.

5.1 Results

The effects of propafenone, lidocaine, quinidine, d-sotalol and ouabain.

In the panels A-D of figure 5.1 the effects of propafenone, lidocaine, quinidine and d-sotalol on the refractory period, conduction velocity and wavelength of premature beats with varying prematurity are plotted. Mean values of measurements carried out in the left part of Bachmann's bundle are given. The number of observations for each drug are given below. Control values (N=18) are represented by the interrupted line. In all situations the basic pacing interval was 350 ms. All drugs significantly

Figure 5.1: The effects of propafenone (N=5), lidocaine (N=11), quinidine (N=14) and d-sotalol (N=4) on the left part of Bachmann's bundle. The refractory period, conduction velocity and wavelength of premature beats are measured at different degrees of prematurity. The interrupted line represents control values (N=18). See text for description.

prolonged atrial refractoriness (29-41% for regular impulses (coupling interval 350 ms) and 45-54% for early premature beats). The effects on conduction velocity however were markedly different.

Propafenone (panel A, N=5) depressed conduction of a normal impulse (right end of curves) to such extent that the prolonging effect on the refractory period was completely neutralized and consequently the wavelength during a normal rhythm remained unchanged. At shorter coupling intervals the depression of conduction velocity was even more pronounced, whereas the prolongation of refractoriness became less. As a result the wavelength of premature beats shortened sharply and at coupling intervals below 275 ms the wavelength was actually shorter than during control. However, because the shortest possible coupling interval was prolonged by propafenone, the shortest wavelength that could be attained was not changed by this drug. During control the shortest wavelength was 6.6 cm at a minimal coupling interval of 114 ms, whereas during propafenone the shortest wavelength was 6.8 cm at an earliest possible prematurity of 148 ms.

The effects of lidocaine (panel B, N=11) were qualitatively similar. However, the degree of slowing of propagation did not completely counter-balance the increased refractoriness during a normal rhythm. Consequently the wavelength of a basic impulse was prolonged by 18%. At shorter coupling intervals this balance was reversed and at a prematurity of less than 225 ms the wavelength became shorter than during control. However also during lidocaine the minimal coupling interval had been increased (147 ms), and therefore the shortest possible wavelength during lidocaine was slightly but significantly longer than during control and amounted to 7.3 cm.

Quinidine (panel C, N=14) prolonged the wavelength of the impulse by 22% during regular beating, because the increase of refractoriness was stronger than the decrease of conduction velocity. At shorter coupling intervals the conduction velocity became relatively more affected and consequently the wavelength prolongation by quinidine became less pronounced. However, also at the shortest possible coupling interval (153 ms) the prolongation of refractoriness exceeded the depression of conduction velocity and as a result quinidine prolonged the shortest wavelength to 9.1 cm, an increase by 38%.

The experimental class III drug d-sotalol (panel D, N=4) exerted the least effect on conduction velocity. During regular pacing the speed of

Figure 5.2: Comparison of the effects of propafenone (■), lidocaine (●), quinidine (▼) and d-sotalol (★) on refractory period, conduction velocity and wavelength of premature beats as measured in the left part of Bachmann's bundle. Control values are represented by the interrupted line. At coupling intervals shorter than 250 ms all drugs prolonged RP to comparable values. However, propafenone and lidocaine depressed conduction to a markedly higher extent than quinidine and d-sotalol. As a consequence, the shortest possible WL was not changed by propafenone and lidocaine, but profoundly prolonged by quinidine and d-sotalol.

propagation was not affected at all and therefore the drug's action on the wavelength was solely determined by its effect on the refractory period. At shorter coupling intervals the prematurity dependent decrement of refractoriness and conduction velocity caused a less pronounced prolongation of the wavelength. However, at the earliest premature beat the maximal depression of conduction was not stronger than during control (to 81 and 82 cm/s, respectively), and consequently also d-sotalol's effect on the wavelength of the shortest coupled extrasystole was only determined by its marked prolongation of refractoriness. Of all drugs tested d-sotalol was the most powerful compound to prevent impulses with a short wavelength in the atrium. During the administration of d-sotalol the shortest wavelength that could be attained was 9.6 cm.

For comparison the effects of the four drugs are plotted together in figure 5.2. It can be seen that the different actions of these drugs on the wavelength of early premature beats (coupling interval <250 ms) is primarily based on the degree of conduction depression. While all drugs exerted comparable effects on refractoriness, propafenone and lidocaine slowed propagation of the impulse to a much higher extent than quinidine and d-sotalol. As a consequence, the shortest attainable wavelength (6.6 cm) was hardly changed during lidocaine (7.3 cm) and propafenone (6.8 cm), whereas a marked prolongation was noted by quinidine (9.1 cm) and d-sotalol (9.6 cm).

Ouabain (N=11) had little effect on the length of the atrial excitation wave. Refractory period was reduced by 6%, probably due to the indirect vagal stimulating effect of the drug, whilst the conduction velocity remained unchanged. This resulted in a slight reduction of the wavelength.

In table 5.1 the statistical data of the effects of propafenone, lidocaine, quinidine, d-sotalol and ouabain on RP, CV and WL during normal rhythm, early premature beats and rapid pacing are given for four atrial sites (right and left part of Bachmann's bundle and the right and left atrial free wall). The relative changes in electrophysiological properties by the various drugs showed only small variations at these different sites. Furthermore it can be concluded that the effects of the different drugs during rapid pacing are comparable to their actions during a normal rhythm. Both propafenone and lidocaine had little effect on the wavelength during a rapid rhythm (reduction of $\pm 7\%$ and an increase of $\pm 5\%$ respectively), while

quinidine and d-sotalol both profoundly prolonged the wavelength by $\pm 33\%$.

The bar charts in figure 5.3 summarize the effects of different cardio-active drugs on the wavelength during normal rhythm (350 ms interval), pacing at the shortest possible driving interval and during the earliest premature beat. The results of acetylcholine (presented in chapter IV), propafenone, lidocaine, quinidine, d-sotalol and ouabain as determined in the left part of Bachmann's bundle are shown.

Figure 5.3: Effect of various drugs on the length of the excitation wave during normal rhythm (350 ms interval), the earliest premature beat and at the maximal pacing rate as measured in the left part of Bachmann's bundle. During normal rhythm the wavelength varied from 10.2 cm during acetylcholine (ACh) to 19.9 cm during d-sotalol. The WL of the earliest premature beat ranged from 5.3 cm (ACh) to 9.6 cm (d-sotalol). Pacing at the maximal rate shortened the WL to a smaller extent during the various circumstances (from 7.5 to 11.7 cm during propafenone and quinidine, respectively).

Table 5.I

The effects of several cardio-active drugs on Refractory Period (RP),
Conduction Velocity (CV) and Wavelength (WL) at four atrial sites.

BB Right	Regular Rhythm			Earliest Premature Beat			Maximal Pacing Rate				
	N	RP (ms)	CV (cm/s)	WL (cm)	RP (ms)	CV (cm/s)	WL (cm)	N	RP (ms)	CV (cm/s)	WL (cm)
Control	15	133±7	133±12	17.7±1.7	99±7	107±13	10.7±1.7	11	106±8	115±13	12.3±2.0
Propafenone	5	164±13 ^{***}	105±9 ^{***}	17.2±1.3	125±4 ^{***}	77±4 ^{***}	9.5±0.4	5	129±9 ^{***}	85±6 ^{***}	11.0±2.0
Lidocaine	12	158±12 ^{***}	121±11 ^{**}	19.1±2.0 [*]	125±14 ^{***}	85±11 ^{***}	10.5±1.0	9	134±15 ^{***}	95±12 ^{**}	12.8±2.5
Quinidine	14	176±16 ^{***}	119±11 ^{**}	20.9±2.7 ^{***}	141±19 ^{***}	97±10 [*]	13.6±1.5 ^{***}	9	145±9 ^{***}	102±9 [*]	14.8±1.6 ^{**}
d-Sotalol	4	180±12 ^{***}	129±6	23.2±2.1 ^{***}	131±4 ^{***}	104±9	13.7±1.3 ^{**}	4	140±5 ^{***}	109±6 ⁻⁻⁻	15.2±0.5 ^{***}
Ouabain	9	124±10 ^{**}	133±7	16.5±1.0	89±6 ^{***}	110±16	9.7±1.3				
BB Left											
Control	18	114±7	127±10	14.5±1.7	80±7	82±6	6.6±0.5	13	89±5	89±14	7.9±1.2
Propafenone	5	148±12 ^{***}	99±8 ^{***}	14.6±1.0	116±17 ^{***}	59±5 ^{***}	6.8±0.6	5	109±4 ^{***}	69±10 ^{**}	7.5±1.1
Lidocaine	11	147±11 ^{***}	118±9 ^{**}	17.2±1.7 ^{***}	123±12 ^{***}	61±8 ^{***}	7.3±0.7 ^{***}	11	120±6 ^{***}	72±14 [*]	8.7±1.7
Quinidine	14	153±9 ^{***}	115±10 ^{**}	17.7±1.6 ^{***}	120±11 ^{***}	76±10	9.1±1.3 ^{***}	9	129±10 ^{***}	90±11 ^{***}	11.7±1.9 ^{***}
d-Sotalol	4	161±19 ^{***}	123±4	19.9±2.6 ^{***}	119±5 ^{***}	81±5	9.6±0.9 ^{***}	4	121±7 ^{***}	90±10 ^{***}	10.9±1.5 ^{***}
Ouabain	11	107±5 [*]	124±8	13.3±0.8 [*]	81±6	81±9	6.6±1.1				

Table 5.I continued.

FW Right	Regular Rhythm				Earliest Premature Beat				Maximal Pacing Rate			
	N	RP (ms)	CV (cm/s)	WL (cm)	RP (ms)	CV (cm/s)	WL (cm)	N	RP (ms)	CV (cm/s)	WL (cm)	
Control	15	124 $\pm$ 9	123 $\pm$ 13	15.2 $\pm$ 1.5	92 $\pm$ 7	83 $\pm$ 8	7.6 $\pm$ 1.0	10	100 $\pm$ 7	95 $\pm$ 16	9.5 $\pm$ 2.0	
Lidocaine	15	159 $\pm$ 9 ^{***}	112 $\pm$ 9 ^{**}	17.7 $\pm$ 1.0 ^{***}	133 $\pm$ 9 ^{***}	62 $\pm$ 13 ^{***}	8.2 $\pm$ 1.7	9	110 $\pm$ 7 ^{***}	87 $\pm$ 6 ^{**}	9.6 $\pm$ 0.8	
Quinidine	10	154 $\pm$ 11 ^{***}	114 $\pm$ 15	17.6 $\pm$ 2.5 ^{**}	125 $\pm$ 15 ^{***}	83 $\pm$ 7	10.4 $\pm$ 1.2 ^{***}	8	145 $\pm$ 27 ^{***}	95 $\pm$ 9	13.8 $\pm$ 2.8 ^{**}	
Ouabain	10	106 $\pm$ 11 [*]	117 $\pm$ 9	13.3 $\pm$ 0.8 ^{**}	78 $\pm$ 10 ^{**}	80 $\pm$ 6	6.3 $\pm$ 0.6					
FW Left												
Control	4	111 $\pm$ 7	132 $\pm$ 9	14.7 $\pm$ 1.9	81 $\pm$ 6	95 $\pm$ 7	7.7 $\pm$ 0.7	4	88 $\pm$ 4	105 $\pm$ 6	9.4 $\pm$ 0.7	
Propafenone	4	138 $\pm$ 15 [*]	115 $\pm$ 12	15.8 $\pm$ 2.1	107 $\pm$ 16 [*]	77 $\pm$ 9 [*]	8.1 $\pm$ 0.7	4	104 $\pm$ 5 ^{**}	84 $\pm$ 11 ^{**}	8.8 $\pm$ 1.2	
Lidocaine	4	148 $\pm$ 14 ^{**}	113 $\pm$ 6 [*]	16.7 $\pm$ 2.0	120 $\pm$ 10 ^{***}	73 $\pm$ 5 ^{**}	8.7 $\pm$ 0.5 [*]	4	110 $\pm$ 7 ^{**}	87 $\pm$ 6 ^{**}	9.6 $\pm$ 0.8	
Quinidine	4	146 $\pm$ 9 ^{***}	128 $\pm$ 15	18.8 $\pm$ 3.0	105 $\pm$ 7 ^{**}	90 $\pm$ 10	9.5 $\pm$ 1.1 [*]	4	114 $\pm$ 3 ^{***}	104 $\pm$ 18	12.0 $\pm$ 2.4	
d-Sotalol	4	148 $\pm$ 13 ^{**}	130 $\pm$ 4	19.3 $\pm$ 1.9 [*]	108 $\pm$ 8 ^{**}	98 $\pm$ 10	10.4 $\pm$ 1.1 [*]	4	111 $\pm$ 11 ^{**}	116 $\pm$ 14	13.0 $\pm$ 2.8 ^{**}	
Ouabain	4	109 $\pm$ 14	139 $\pm$ 8	15.3 $\pm$ 2.6	80 $\pm$ 7	94 $\pm$ 10	7.5 $\pm$ 1.2					

BB Right = Right Part Bachmann Bundle

BB Left = Left Part Bachmann Bundle

FW Right = Free Wall Right Atrium

FW Left = Free Wall Left Atrium

*** = p<0.001

** = p<0.01

* = p<0.05

Effects of propafenone, lidocaine, quinidine, d-sotalol and ouabain on the cycle length of atrial tachy-arrhythmias.

Figure 5.4, upper panel, shows the change of the beat to beat interval of an episode of atrial flutter following the start of a continuous infusion of lidocaine. A gradual increase in cycle length from ± 95 ms to ± 122 ms can be noted. During the lidocaine infusion the interval remained near the latter value and the flutter was not interrupted. This effect of lidocaine on atrial flutter was highly reproducible and similar results were obtained during administration of propafenone. The lower panel of fig. 5.4 shows the effect of the administration of d-sotalol on the beat to beat

Figure 5.4: The influence of two drugs which prolonged refractoriness (lidocaine and d-sotalol) on the beat to beat interval and stability of atrial flutter. Shortly after the start of a continuous infusion of lidocaine (which hardly affected the wavelength during rapid rhythm) the flutter interval gradually increased from 95 to 128 ms. After a period of stabilization the flutter continued at the decreased rate. Although more slowly, also the administration of d-sotalol resulted in a gradual increment of the interval of an another period of atrial flutter. However during this drug, which markedly prolonged the WL, the flutter did not continue at a slower rate. When the interval had increased to about 120 ms, the flutter was interrupted and sinus rhythm resumed.

interval of another period of atrial flutter. Although the prolonging effect of d-sotalol on the flutter interval set in more slowly, it became increasingly progressive until after about 4 minutes the flutter was interrupted and sinus rhythm resumed. This response to d-sotalol was also representative for the action of quinidine on atrial flutter. Table 5.II gives the observed changes in cycle length or number of conversions of atrial flutter by the different drugs. Both propafenone and lidocaine caused a prolongation of the flutter cycle length by about 35%. In only one instance conversion to sinus rhythm was observed. On the other hand, administration of either quinidine or d-sotalol was a highly successful method for termination of atrial flutter. Quinidine failed only once to interrupt an episode of atrial flutter. In this case the cycle length was prolonged to 160 ms. In two of the three cases in which ouabain was administered during a period of atrial flutter, degeneration into atrial fibrillation was observed.

Table 5.II Change in cycle length or interruption of atrial flutter by five different cardio-active drugs.

	<u>N</u>	<u>Cycle length (ms)</u>		<u>Interruption of flutter</u>
		before drug	after drug	
Propafenone	4	89 $\pm$ 4	120 $\pm$ 9	0 (0%)
Lidocaine	7	94 $\pm$ 7	126 $\pm$ 10	1 (14%) SR
Quinidine	7	96 $\pm$ 5	160	6 (86%) SR
d-Sotalol	4	91 $\pm$ 3	-	4 (100%) SR
Ouabain	3	94 $\pm$ 3	87	2 (67%) AFib

SR = Sinus Rhythm
AFib = Atrial Fibrillation

An example of the action of lidocaine on the cycle length during atrial fibrillation is shown in figure 5.5. During an episode of stable fibrillation lidocaine was administered, which did not terminate the arrhythmia. The upper tracing shows a local recording of fibrillation during control, the lower tracing was recorded during the administration of lidocaine. The time scales are the same. Both tracings show the varying morphology and time spacing of electrograms, characteristic of fibrillation. The intervals between the consecutive activations are clearly longer during lidocaine than during control. Consequently the number of activations per unit of time (and thus the rate of fibrillation) during lidocaine was lower. In four dogs we determined the mean rate of atrial fibrillation before and during the administration of lidocaine. The rate of fibrillation was profoundly decreased from 833 ± 81 per minute during control to 480 ± 72 /min during lidocaine. During the administration of quinidine or d-sotalol we also observed an initial decrement of the rate of atrial fibrillation. However, the slowing of the rate never stabilized but continued progressively until the fibrillatory process was interrupted. The success rate of quinidine and d-sotalol in converting atrial fibrillation to sinus rhythm was 100%.

LOCAL RECORDINGS OF ATRIAL FIBRILLATION

Figure 5.5: The influence of lidocaine on atrial fibrillation rate. Local recordings of fibrillation during control (panel A) and lidocaine (panel B) are shown. Activation time intervals are given below the tracings, V denotes a ventricular complex. Both recordings show the varying morphology and time spacing of electrograms, characteristic of fibrillation. However, during lidocaine activation intervals were much longer than during control. Thus lidocaine strongly decreased the mean fibrillation rate (N=4 dogs) from 833 to 480 per minute.

5.3 Discussion

Effects of drugs on atrial electrophysiology and anti-arrhythmic efficacy.

Prolongation of refractoriness is widely held as an important anti-arrhythmic feature (Calan et al. 1976, Dhingra et al. 1976, Ledda et al. 1981, Bennett 1982, Platou et al. 1982) and measurement of refractory periods is common practice in clinical electrophysiological drug testing. However, according to the wavelength principle, pharmaceutical lengthening of the refractory period will only be advantageous in the interruption or prevention of reentrant arrhythmias if it is accompanied by an increase of the wavelength, which is given by the product of both RP and CV (Lewis et al. 1925, Smeets 1983, Wellens et al. 1984). The results of our studies on four drugs which profoundly increased atrial refractoriness (propafenone, lidocaine, quinidine and d-sotalol) show that such an action does not necessarily prolong the length of the atrial excitation wave. Propafenone depressed the speed of propagation of a regular impulse to such extent that the prolongation of the refractory period was completely counterbalanced, and consequently the wavelength remained unchanged. The same effect was observed during early premature beats and rapid pacing. A similar strong depressant effect on intra-atrial conduction by the same dosage of propafenone was reported by Karagueuzian et al. (1984). The high doses of lidocaine we used also had opposite effects on refractoriness and conduction velocity, leaving the wavelength of early premature beats and during rapid pacing almost unchanged.

The two other drugs which prolonged refractoriness exhibited much less effect on the speed of propagation of the impulse. The minimal values of conduction velocity as measured during the earliest premature beat and during rapid pacing were only slightly lower (quinidine) or unaltered (d-sotalol) as compared to control. Therefore the effects of these drugs on the wavelength were mainly determined by their action on the refractory period. Consequently, these drugs dramatically prolonged the wavelength. This action was present during slow and rapid pacing and during early premature beats.

The effects of drugs on the wavelength of early premature beats may be helpful in determining their effectiveness in the prevention of atrial tachy-arrhythmias. With a long wavelength a large area of conduction block

is needed to make a first reentrant loop possible. Since the occurrence of a large continuous area of unidirectional block is highly improbable, an increase of the wavelength of premature beats can be expected to prevent the initiation of reentrant circuits. In chapter VI the wavelength of early premature beats will be correlated to the inducibility of atrial tachy-arrhythmias. Determination of drug effects on the wavelength during rapid pacing may also be of importance to predict their usefulness in the interruption of atrial tachy-arrhythmias. An increase in the size of a reentrant circuit by a prolongation of the wavelength will force the impulse into refractory tissue or the anatomical boundaries of the atria. Consequently, the circuit and thus the tachy-arrhythmia will be interrupted. Also during atrial fibrillation an increase of circuit size will be beneficial by reducing the number of circulating impulses. When a critical minimal number necessary to maintain fibrillation is reached, the chance of simultaneous extinction of the present wavefronts becomes very high and thus the fibrillatory proces is likely to stop (Moe et al. 1959, Allesie et al. 1985).

Our observations on the behaviour of atrial tachy-arrhythmias during the administration of different drugs are in good agreement with these considerations. The two agents (lidocaine and propafenone) which increased refractoriness without affecting the wavelength during rapid pacing, both exhibited very poor anti-arrhythmic effects. Furthermore, the observed decrease in atrial fibrillation rate by lidocaine supports the concept that multiple functional reentrant circuits form the basis of this arrhythmia. In contrast, the combined profound prolongation of refractoriness and wavelength during rapid rhythms by quinidine and d-sotalol readily explains the observed high conversion rates of atrial flutter (85-100%) and atrial fibrillation (100%) by these drugs.

Our observations are also in accordance with the clinical effectiveness of the different drugs in treating or preventing atrial flutter and fibrillation. For instance, the usefulness of propafenone for the treatment of patients with atrial flutter or fibrillation is quite controversial. Although some studies report success rates from 60 to 80% (Kerr et al. 1985, Hammill et al. 1985), others achieved conversion to sinus rhythm in only 20 to 27% of patients (Beck et al. 1978, Connolly et al. 1985, Kersschot et al. 1985), although a significant increase in atrial refractoriness was noted (Kersschot et al. 1985). Also lidocaine has been shown

to be ineffective in the termination of human atrial flutter or fibrillation (Grossmann et al. 1968, Flensted-Jensen et al. 1969). On the other hand, the longtime clinical experience with quinidine has proven it to be a potent drug in the treatment of atrial tachy-arrhythmias. Already shortly after the introduction of this drug for these purposes a success rate of 50% had been mentioned (Frey 1921). In a survey of the more recent literature on treatment of atrial fibrillation, Campbell (1982) reports a 3-month maintenance of sinus rhythm in 59-75% and a 1-year maintenance rate of 24-74% in treated patients, versus 34-56% and 0-56% respectively in control subjects. The failure of quinidine to prevent relapses of atrial fibrillation in some patients might be related to a more outspoken depression of the conduction velocity, resulting in a smaller (or no) prolongation of the wavelength. Or, as Lewis put it in 1921: "The two effects of quinidine are opposed in so far as they influence the termination or continuation of circus movement. While we attribute the frequent abolition of clinical fibrillation by quinidine to a predominant influence upon the refractory period, we attribute its equally frequent failure to end the fibrillation to its balancing or predominating influence on conduction." In this respect the experimental drug d-sotalol is very promising for the treatment of atrial reentrant arrhythmias, because in our experiments this compound showed the least effects of all drugs tested on conduction properties in the atrium.

The last cardioactive drug tested, ouabain, caused a small reduction of atrial refractoriness and concomitantly of the wavelength. It exhibited no anti-arrhythmic effects; in contrast, in two instances degeneration of atrial flutter into fibrillation was observed. Ouabain's shortening of the wavelength can account for this phenomenon. The shorter the wavelength, the more reentering impulses can simultaneously exist, thus promoting the occurrence of atrial fibrillation. The decrease of atrial refractoriness by cardiac glycosides is probably due to changes in vagal influence. Although in isolated or denervated hearts these compounds prolong atrial refractoriness (Mendez et al. 1953), in the intact animal they modify atrial electrophysiology by sensitizing the heart to vagal stimulation (Gaffney et al. 1973). Thus atrial refractory period is shortened and AV conduction prolonged by cardiac glycosides when vagal innervation is intact (Mendez et al. 1953). In dogs with the Rosenblueth/Garcia Ramos type flutter and

intact vagi, Farah and Loomis (1950) found that ouabain administration often changed the flutter into fibrillation. Only when the vagi were cut or after the administration of atropine the flutter converted to sinus rhythm. In humans ouabain is often used to slow the ventricular rate in the presence of atrial flutter or fibrillation. However it seldom restores sinus rhythm and often degeneration of atrial flutter into fibrillation is observed. If however ouabain is used for the treatment of decompensated hearts, the increased myocardial contractility can decrease atrial size. Atrial fibrillation in this setting may be stopped by ouabain.

Functional or anatomical reentry in canine flutter?

The effects of lidocaine and d-sotalol on the cycle length and stability of atrial flutter are illustrated in figure 5.4. Both agents prolonged atrial refractoriness to the same extent. However, because of its depressant effect on conduction, lidocaine left the wavelength unchanged. This drug did not interrupt the flutter, but merely increased its cycle length by about 30%. An increase in cycle length by lidocaine has also been observed in human atrial flutter (Danahy et al. 1978). Also d-sotalol caused a gradual and marked increase of the flutter interval. In addition to RP lengthening however, this compound also prolonged the wavelength markedly. As a result the atrial flutter was converted to sinus rhythm. The question arises whether the increase of the flutter interval by these drugs which prolong refractoriness allows any conclusions about the type of reentry involved (functional or anatomical). The revolution time of a functionally determined circuit is known to be prolonged by an increase of RP (Allessie et al. 1977). The depression of CV by lidocaine may be expected to increase the cycle length of flutter based on anatomically determined reentry as well. However, it is likely that RP prolongation by d-sotalol may also increase the revolution time of "anatomical" reentry. Because this drug did not affect CV, the wavelength was prolonged. Consequently, the fully excitable gap in an "anatomical" circuit would become smaller and finally partially excitable. This will lead to a slowing of the conduction velocity of the circulating impulse and consequently to a prolongation of the revolution time. Therefore, we believe that it is hazardous to make inferences about the type of reentry on the basis of observed changes in cycle length by RP prolonging drugs.

CHAPTER VI

THE WAVELENGTH OF THE ATRIAL IMPULSE AS AN INDEX FOR THE INDUCTION OF REENTRANT ARRHYTHMIAS

In the preceding chapters we have described the effects of several interventions (variations in rate and rhythm, modulation of autonomic tone, administration of cardio-active drugs) on the length of the atrial excitation wave in chronically instrumented dogs. To determine the role of various electrophysiological parameters in the occurrence of arrhythmias, in this chapter we will correlate refractory period, conduction velocity and wavelength to the induction of rapid repetitive responses, atrial flutter and atrial fibrillation. On the basis of this analysis, we conclude that the refractory period and the conduction velocity alone are unreliable indicators for the susceptibility to arrhythmias. In contrast, the length of the excitation wave turned out to be a good index of the vulnerability of the atrium to various arrhythmias under a wide range of circumstances.

The analysis presented in this chapter is based on a population of 750 early premature impulses with a relative prematurity from 0-50 ms. The observations were made during control and during the administration of acetylcholine, propafenone, lidocaine, quinidine, d-sotalol and ouabain. Table 6.I gives the number of observed responses (No Arrhythmias, Rapid Repetitive Responses, Atrial Flutter and Atrial Fibrillation) in the respective situations. During control the induction of a premature impulse most frequently (38%) resulted in a series of rapid repetitive responses. No arrhythmias (21%) and atrial fibrillation (24%) occurred less often, whereas atrial flutter (16%) had the lowest frequency of occurrence. The administration of acetylcholine dramatically changed this pattern. In this situation, no less than 73% of extrasystoles elicited episodes of atrial fibrillation. The parasympathetic agent also increased the relative incidence of another sustained tachy-arrhythmia, atrial flutter (12%), as compared to RRR (10%) and No Arr (6%). Propafenone did not have much effect on atrial susceptibility to the different arrhythmias, the relative fre-

Table 6.1 Number of observed arrhythmias induced by early premature beats during control and during the administration of various cardio-active drugs.

	<u>Dogs</u>	<u>No Arr</u>	<u>RRR</u>	<u>AFI</u>	<u>AFib</u>	<u>N</u>
Control	19	32 (21%)	57 (38%)	24 (16%)	36 (24%)	149
Acetylcholine	17	8 (6%)	14 (10%)	17 (12%)	106 (73%)	145
Propafenone	5	9 (17%)	22 (42%)	10 (19%)	12 (23%)	53
Lidocaine	19	37 (23%)	52 (32%)	41 (26%)	29 (18%)	159
Quinidine	16	73 (62%)	36 (31%)	8 (7%)	-	117
d-Sotalol	4	31 (80%)	8 (20%)	-	-	39
Ouabain	10	11 (13%)	34 (39%)	18 (20%)	25 (28%)	<u>88</u>

750

quencies of No Arr, RRR, AFI and AFib being 17%, 42%, 19% and 23% respectively. During lidocaine the occurrence of AFI was increased (26%) at the cost of AFib (18%) and RRR (32%). Both quinidine and d-sotalol exerted profound anti-arrhythmic effects. During quinidine no cases of AFib were observed, AFI and RRR occurred in only 7 and 31% respectively, whereas the far majority (62%) of premature beats did not result in atrial arrhythmias. The anti-arrhythmic effect of d-sotalol was even stronger. Sustained atrial arrhythmias (AFib or AFI) could not be elicited during the administration of this compound. Eighty percent of premature beats did not disturb the normal rhythm and in only 20% RRR were seen. During ouabain, finally, a slight increase in the incidence of both AFib and AFI was observed.

In figure 6.1 cumulative histograms of all events of atrial fibrillation (N=208), atrial flutter (N=118), rapid repetitive response (N=223) and no arrhythmias (N=201) are plotted in relation to RP, CV and WL. The height of

Figure 6.1: Cumulative histograms of the occurrence of No Arrhythmias (No Arr), Rapid Repetitive Responses (RRR), Atrial Flutter (AFL) and Atrial Fibrillation (AFib) in relation to the refractory period (RP), conduction velocity (CV) and wavelength (WL) of early premature impulses as determined during control and during the administration of various drugs (see text). The height of each bar represents the total number of observations per class while the different shadings indicate the relative number per sub-population. All histograms show a certain amount of overlap. However in case of the WL the four different subgroups clearly have the most narrow and separated histograms, indicating that the wavelength is the best discriminating index for the occurrence of the different arrhythmias. The critical values of RP, CV and WL for AFib, AFL and RRR as computed by discriminant analysis, are indicated by arrows.

each bar represents the total number of observations in each class, whilst the different shadings indicate the relative number of the various responses (AFib, AF1, RRR and No Arrhythmias). A striking characteristic of the different histograms is the considerable overlap between the four types of response. No complete separation between the subpopulations can be seen. However, the degree of overlap was markedly different for RP, CV and WL. The amount of overlapping was highest for the conduction velocity and less but still considerable for the refractory period. The wavelength showed a good discrimination, the cumulative histogram showing the least overlap between the different arrhythmias. The arrows in the histograms indicate the critical values of the electrophysiological parameters for AFib, AF1 and RRR as computed by discriminant analysis (see chapter II). The critical values of the RP for AFib, AF1 and RRR were respectively 93, 108 and 121 ms and of CV 87, 93 and 103 cm/s. The critical wavelength value for AFib was 7.8 cm, for AF1 9.7 cm and for RRR 12.3 cm. Discriminant analysis expresses the degree of discrimination of these parameters in the predictive power

Table 6.II Predictive power of Refractory Period, Conduction Velocity and Wavelength for the induction of different atrial arrhythmias.

	<u>N</u>	<u>Refractory</u> <u>Period</u>	<u>Conduction</u> <u>Velocity</u>	<u>Wave-</u> <u>Length</u>
Fibrillation	208	79%	57%	82%
Flutter	118	15%	9%	73%
Rep. Responses	223	17%	18%	65%
No Arrhythmias	<u>201</u>	<u>68%</u>	<u>57%</u>	<u>80%</u>
Overall correct classification	750	<u>48%</u>	<u>38%</u>	<u>75%</u>

for each of the four types of responses (AFib, AF1, RRR and No Arrhythmias, table 6.II). Also the sensitivity and specificity of RP, CV and WL for the induction of the different arrhythmias are calculated (table 6.III). The results clearly show that the wavelength of the atrial impulse is the best predictor for the occurrence of arrhythmias, with a correct classification of 65-82% for the different types of response. Both conduction velocity and refractory period had a much lower predictive power (15-79% and 9-57% respectively). The overall correct prediction of the occurrence of the different responses was: Refractory Period 48%, Conduction Velocity 38% and Wavelength 75%. The wavelength was also the most sensitive (88-100%) and specific (80-96%) index for the induction of the various arrhythmias. Thus it may be concluded that refractory period and conduction velocity are rather poor indicators for the occurrence of atrial arrhythmias and that the wavelength is a preferable parameter to predict the vulnerability to reentrant arrhythmias.

Table 6.III

Sensitivity and specificity of RP, CV and WL for the occurrence of atrial arrhythmias.

		<u>Refractory Period</u>	<u>Conduction Velocity</u>	<u>Wave- Length</u>
Fibrillation versus No Arrhythmias	<u>Sens:</u>	84%	71%	100%
	<u>Spec:</u>	89%	72%	96%
Flutter versus No Arrhythmias	<u>Sens:</u>	65%	75%	100%
	<u>Spec:</u>	72%	70%	89%
Rep. Responses versus No Arrhythmias	<u>Sens:</u>	67%	66%	88%
	<u>Spec:</u>	68%	57%	80%
All Arrhythmias versus No Arrhythmias	<u>Sens:</u>	69%	68%	88%
	<u>Spec:</u>	76%	70%	89%

In figure 6.2 the values of RP, CV and WL of all observations are plotted together. Panel A is the key to the other panels. RP is plotted on the abscissa and CV on the ordinate. Since the value of the wavelength is given by the product of RP and CV, iso-wavelength curves can be drawn which are plotted for WL values from 4 to 20 cm. In panel B all the individual cases (No Arr, RRR, AF1 and AFib, N=750) as observed during control and drug studies are plotted. The observed range of RP was from 50 to 160 ms, of CV from 50 to 160 cm/s and of the wavelength from 4 to 22 cm. In panels C through F the observations are plotted separately for the different responses. Panel C gives the cases in which no arrhythmias were induced, the critical wavelength for the induction of arrhythmias being 12.3 cm. In panel D the rapid repetitive responses are plotted, the critical zone for the occurrence of RRR lying between 12.3 and 9.7 cm (predictive power 65%). Also in case of atrial flutter and atrial fibrillation (panels E and F) there was a narrow range of WL in which these arrhythmias occurred. The critical wavelength for AF1 was 9.7 cm, and for AFib 7.8 cm. Seventy-three percent of the cases of AF1 fell in the wavelength zone demarcated by these two values, whereas in 82% of AFib the WL was shorter than 7.8 cm. Thus, this figure illustrates that each type of atrial response could be elicited at a wide range of both RP and CV, but at only a narrow wavelength zone.

In figure 6.3 the critical values of RP, CV and WL for the induction of arrhythmias are determined during the administration of various drugs. The critical value of the refractory period for the induction of RRR ranged from 87 ms during acetylcholine administration to 134 ms during lidocaine infusion. For atrial flutter these values were 80 and 129 ms and for the induction of fibrillation 70 and 127 ms. Also the critical value of the conduction velocity for the three arrhythmias exhibited a wide variation during the different interventions and ranged from 92 to 123 for RRR, from 79 to 121 for flutter and from 65 to 110 cm/s for fibrillation. In contrast, the critical value of the wavelength for the induction of arrhythmias was markedly constant despite the various strong changes in electrophysiological properties exerted by the different drugs. For the induction of RRR the critical value of the wavelength during control was 11.7 cm, during acetylcholine 11.8 cm, propafenone 11.9 cm, lidocaine 12.6 cm, ouabain 12.0 cm, quinidine 12.6 cm and d-sotalol 12.0 cm. For atrial flutter the critical wavelength values were respectively 9.2, 9.6, 9.7, 10.1, 9.6, and 9.8 cm. Because AF1 could not be induced during d-sotalol, no

Figure 6.2: Relationship between the induction of atrial arrhythmias and refractory period (RP), conduction velocity (CV) and wavelength (WL) of early premature beats. Panel A gives the format of all panels. RP is plotted on the abscissa and CV on the ordinate. Because the WL is given by the product of RP and CV, iso-wavelength curves can be drawn. In panel B all individual observations (N=750) are plotted in this manner. In the lower four panels the four different subpopulations have been plotted separately together with their respective critical wavelengths. The different responses were observed in almost the total range of measured RP and CV values. However, rather narrow zones of WL could be identified for the induction of the various arrhythmias. Sixty-five percent of observations of RRR occurred at a WL range from 12.3 to 9.7 cm, 73% of Atrial Flutter at a WL zone from 9.7 to 7.8 cm, whereas in 82% of cases of Atrial Fibrillation WL was shorter than 7.8 cm.

Figure 6.3: Critical values of refractory period (RP), conduction velocity (CV) and wavelength (WL) for the induction of Rapid Repetitive Responses (■), Atrial Flutter (▼) and Atrial Fibrillation (●) as determined during control and the administration of various drugs. Ach denotes acetylcholine. Critical values of both RP and CV for the different arrhythmias varied widely under these circumstances. However, the critical value of WL for the three types of arrhythmias was remarkably constant in all different situations.

critical value is given. For atrial fibrillation the respective critical wavelengths measured 7.5, 7.7, 8.1, 8.2 and 7.8 cm. Both quinidine and d-sotalol prevented the occurrence of this arrhythmia.

In conclusion, the small critical zones of WL for the induction of atrial arrhythmias, the high predictive power of WL and the stability of the critical WL values under highly different circumstances, all strongly suggest that the length of the atrial impulse is an important variable for the initiation of atrial reentrant arrhythmias and should be considered an useful index of the vulnerability of the heart to these arrhythmias.

CHAPTER VII

GENERAL DISCUSSION

Correlation between wavelength and atrial arrhythmias.

The results presented in the previous chapters show that the length of the atrial excitation wave is an important determinant for the occurrence of atrial arrhythmias. In 19 chronically instrumented awake dogs each studied during a period of maximally two months, a total of 549 episodes of atrial tachy-arrhythmias were induced (Rapid Repetitive Responses (N=223), Atrial Flutter (N=118), Atrial Fibrillation (N=208)). The influence of the autonomic nervous system and several cardiac drugs (quinidine, lidocaine, ouabain, d-sotalol, propafenone) were studied both on the inducibility of arrhythmias and on changes in basic electrophysiological properties.

The duration of the refractory period of atrial myocardium is widely recognized to be an important parameter for the vulnerability of the atria to fibrillation (Andrus et al. 1930, Olsson et al. 1971, Calan et al. 1976, Wyndham et al. 1977, Engel et al. 1978, Michelucci et al. 1982). This has led to the common opinion that agents which prolong refractoriness implicitly have anti-arrhythmic properties (Calan et al. 1976, Dhingra et al. 1976, Hashimoto et al. 1979, Kasper et al. 1979, Bauernfeind et al. 1980, Ledda et al. 1981, Patterson et al. 1981, Bennett et al. 1982, Platou et al. 1982, Vaughan Williams et al. 1984). In our studies we could confirm that under some circumstances indeed there was a good correlation between the duration of the refractory period and the inducibility of arrhythmias. For instance shortening of refractoriness by administration of acetylcholine or the presence of a high vagal tone, clearly favored the induction of atrial tachy-arrhythmias. Likewise, some drugs which prolonged the refractory period, like quinidine and d-sotalol, exhibited a definite anti-arrhythmic effect. However, under other conditions like the administration of lidocaine or propafenone, a clear prolongation of the refractory period did not result in a diminishment of atrial arrhythmias.

Compared to the extensive literature on the relationship between the refractory period and cardiac arrhythmias, reports about the role of the conduction velocity in the occurrence of atrial tachy-arrhythmias are relatively scarce (Leier et al. 1978, Simpson et al. 1982, Cosio et al. 1983, Buxton et al. 1984). These papers agree that abnormalities in P-wave morphology or prolongation in intra-atrial conduction time are major predisposing factors for the development of atrial flutter and fibrillation. In our studies we found a poor correlation between conduction velocity and atrial arrhythmias (predictive power 38%). As described above for the refractory period, also the conduction velocity turned out to be not a very consistent predictor of atrial tachy-arrhythmias. Under some conditions (premature beats or rapid pacing) slowing of conduction did correlate with the occurrence of arrhythmias, but under other circumstances (drugs which depress conduction) either the vulnerability to atrial arrhythmias was unchanged (lidocaine and propafenone) or actually decreased (quinidine).

Compared to the invalidity of either the refractory period or the conduction velocity alone, the combination of both parameters as given by the wavelength of the impulse ($WL = RP \times CV$) turned out to be a good index for the vulnerability to arrhythmias (predictive power 75%). This finding fits with the experimental evidence that atrial arrhythmias like rapid repetitive responses, atrial flutter and atrial fibrillation are based on intra-atrial reentry (Allessie et al. 1977, 1984, 1985, Boineau et al. 1980).

Significance of the wavelength for reentrant mechanisms.

The length of the excitation wave determines the minimal size of a reentrant circuit and thus the size of the block area required for initiation of reentry. In our study, premature beats with a wavelength longer than 12.3 cm rarely induced atrial arrhythmias, independent of the drug administered. A sufficiently large area of conduction block to permit the creation of a circuit of that size obviously does not occur in normal canine atria. Gradual shortening of the wavelength of premature impulses was accompanied by the occurrence of increasingly serious arrhythmias. At a wavelength shorter than 12.3 cm only short bursts of rapid repetitive

activity were observed. This wavelength apparently does not yet permit the existence of a sustained reentrant circuit. The question arises why sometimes only a limited number of repetitive beats is initiated, whilst in other instances sustained atrial flutter is started. An explanation might be that this relatively long wavelength does not allow the set up of a sustained localized circuit, but that instead a single wide activation front wanders through the atria, reentering at different sites before it dies out at the borders of the atria. The varying intervals and complex morphology of local electrograms which are often observed during a run of repetitive activity, could be explained in this way.

At shorter wavelengths (<9.7 cm) paroxysms of flutter occurred. This critical value corresponds with the maximal circumference of intramyocardial circuits, as determined by total mapping of the atrial activation during atrial flutter in isolated canine hearts (Alessie et al. 1984). They reported that during different episodes of atrial flutter the length of functional circuits measured from 5 to 10 cm.

Early premature beats with a wavelength of less than 7.8 cm very frequently induced atrial fibrillation. The duration of these paroxysms of fibrillation varied considerably. Under control conditions (no drugs, vagal state) fibrillation lasted from 10 seconds to several hours (average duration about 3 minutes). Interventions which moderately prolonged the atrial wavelength, like decreasing the vagal tone, clearly shortened the average duration of fibrillation. This decrease of the stability of the fibrillatory process is most likely related to the smaller number of wavelets that can be present in the atria because of the longer wavelength. Drugs which strongly prolong the wavelength of premature beats (quinidine, d-sotalol) did not only terminate fibrillation but also completely prevented the initiation of this arrhythmia. Obviously, if the wavelength is brought above the critical value of 7.8 cm the occurrence of intra-atrial block no longer leads to fibrillation.

In figure 7.1 the relationship between RP, CV and WL and the occurrence of RRR, AF_I and AF_{ib} is summarized. Although these arrhythmias were observed at a wide range of measured values of RP and CV, their occurrence was limited to rather narrow zones of WL, as indicated by the respective critical wavelength curves. The concept of a critical wavelength for reentrant arrhythmias suggests that it might be useful to describe the

Figure 7.1: The induction of Rapid Repetitive Responses, Atrial Flutter and Atrial Fibrillation in relation to the observed values of refractory period (RP), conduction velocity (CV) and wavelength (WL). Each arrhythmia could be elicited at a wide range of measured RP and CV values. However, narrow wavelength zones, delineated by the respective critical wavelengths, could be identified for the induction of the different arrhythmias. It is therefore suggested that effects of cardio-active drugs be described in terms of changes in wavelength.

effects of cardio-active drugs in terms of changes in wavelength. Drugs which shorten the wavelength must be regarded as arrhythmogenic, whereas agents which prolong the wavelength can be expected to possess anti-fibrillatory properties. An increase in WL is most successfully effectuated by a combined increase in RP and CV. Compounds whose action on one of these variables is completely counterbalanced by an opposite effect on the other will exert neither anti-arrhythmic nor arrhythmogenic influence. However, a prolongation of the RP per se might act beneficially by slowing the rate of reentrant arrhythmias. Circumstances which shorten the WL to the flutter and fibrillation zones will clearly favour the occurrence of reentrant arrhythmias. In this respect a simultaneous decrease in RP and CV must be considered highly arrhythmogenic.

Wavelength and tissue mass.

The multiple wavelet theory of fibrillation relates the inducibility and stability of atrial fibrillation to the number of wavelets simultaneously present in a given surface area (Moe et al. 1959, 1962, 1964). To gain more insight in the relationship between wavelength, tissue mass and the occurrence of atrial fibrillation, we estimated the maximal number of wavelets as a function of the wavelength in a certain available tissue surface area. The maximal number of circuits is given by the surface area divided by the area of a circle with a circumference equal to the wavelength (number of circuits = surface area divided by $WL^2/4\pi$). In this simplification the variable shape of the excitation waves, inhomogeneity in wavelength, effect of atrial geometry or the existence of excitable gaps during fibrillation have not been taken into account. In figure 7.2 the maximal number of wavelets in a surface area of 35 cm^2 (which was the average atrial surface area in our study) is plotted as a function of the wavelength. At the critical wavelength for atrial fibrillation (7.8 cm) the atrium could accommodate about 7 wavelets. This corresponds with the number of simultaneous wavelets Allesie et al. (1985) observed during atrial fibrillation in intact canine hearts. By total mapping of the atrial activation during fibrillation, they found that the fibrillatory process was stable with 6 or more simultaneously wandering wavelets, whereas a high chance of termination of the arrhythmia existed when only 3 excitation fronts were present. It may be noticed that the critical wavelength for fibrillation is found at the steep part of the curve, where small changes in wavelength have a large effect on the number of wavelets. Thus, a relatively slight shortening of the wavelength will rapidly increase the maximal number of wavelets, while a minor increase of WL will reduce this number to a value below the fibrillation threshold. This illustrates that there is only a small "safety margin" of the wavelength between atrial fibrillation and sinus rhythm. Indeed we observed that alerting the dog or taking it out for a walk (which was accompanied by a relatively small increase of the wavelength caused by a decrease in vagal tone) very often converted atrial fibrillation to sinus rhythm. It may also explain the markedly increased susceptibility to atrial fibrillation in diseased hearts, in which a shortened wavelength can be expected due to impaired conduction properties. On the other hand, anti-

Figure 7.2: Relationship between wavelength of the impulse and the maximal number of wavelets in the canine atrium. The number of wavelets is given by the atrial surface area (35 cm²) divided by the surface area of one circuit with a circumference equal to the wavelength ($N = 35 \times 4\pi / WL$). At the steep part of the curve, small changes in WL cause large variations in the maximal number of wavelets. The critical number of wavelets for atrial fibrillation as observed by others (Allessie et al. 1985) is indicated by the interrupted line. The point on the curve determined by the critical WL for fibrillation (7.8 cm) falls just above this threshold. A small shortening of the WL dramatically increases the number of wavelets and may be expected to act very arrhythmogenic. On the other hand, anti-arrhythmic drugs which prolong the wavelength will exert antifibrillatory action by reducing the number of intra-atrial circuits.

arrhythmic drugs which prolong the wavelength will markedly reduce the number of intra-atrial circuits and thus be very effective in the treatment of atrial fibrillation.

In figure 7.3 we have estimated the relationship between the WL and the maximal number of intra-atrial wavelets for the atrial surface area of mammals of increasing size. The atrial wavelengths of early premature beats of some species (indicated by stars) have been determined on the basis of known differences and similarities in atrial electrophysiological proper-

ties in mammals of increasing size. Atrial refractoriness shows striking species differences and tends to increase with body size. For instance, the atrial RP during a regular rhythm in the rabbit is 70 ms (Smeets et al. 1986) and in man 220-260 ms (Attuel et al. 1982, Michelucci et al. 1985). There is only sparse information on cardiac electrophysiology of the elephant and whale (White et al. 1938, 1953, King et al. 1953). We used the following RP of early premature beats: rabbit 60 ms, man 150 ms, horse 200 ms, elephant 275 ms and whale 375 ms. In contrast to RP, conduction velocity in the atrium has been reported to show less marked variations in rabbit, cat, dog and goat (Draper et al. 1959, Sommer et al. 1970, Meijler 1985). We estimated the following CV of early premature beats: rabbit 60 cm/s, man 80 cm/s, horse 100 cm/s, elephant 110 cm/s and whale 120 cm/s. On the basis of these values the wavelength of early atrial premature beats in species of increasing body size is calculated to be: rabbit 3.5 cm, dog 8 cm, man 12 cm, horse 20 cm, elephant 30 cm and whale 45 cm. In the rabbit atrium with a surface area of 3 cm^2 , a wavelength of 3.5 cm would enable the simultaneous existence of only three wavelets. The wavelength of premature beats in the canine atrium (8 cm) permits 6 intra-atrial circuits in a surface area of 35 cm^2 . In man the estimated atrial surface area of 60 cm^2 can support maximally 5 wavelets at a WL of 12 cm. In the estimated atrial surface (300 cm^2) of the horse no less than 10 wavefronts could be accommodated, whereas in the elephant and the whale, a wavelength of 30 and 45 cm would allow 13 and 19 wavelets in their respective atria.

When the line indicating the critical number of 6 wavelets for sustained fibrillation is drawn, it can be seen that the rabbit is safely below this threshold, dog and man are dangerously near the fibrillation threshold, whereas horse, elephant and whale are far above this line. This is in good agreement with the stability of atrial fibrillation in the different species. It is a well-known observation that atrial fibrillation in the rabbit heart, if it can be elicited at all, stops almost immediately after its induction (Holland et al. 1957, 1958). In our dogs we were able to elicit episodes of atrial fibrillation lasting from 10 seconds to several hours. Boswell et al. (1968) reported a direct relationship between the size of morphinized but otherwise normal dogs and the duration of experimentally induced fibrillation. In a group of large dogs the episodes of fibrillation lasted from 24 to 150 hours, in the medium sized dogs from several seconds

Figure 7.3: Relationship between atrial wavelength and the maximal number of circuits in the atria of differently sized mammals. The critical number of wavelets for fibrillation (6) is indicated by the interrupted line. Because the prolongation of the wavelength in mammals of increasing size is proportionally less than the enlargement of atrial surface area, the maximal number of wavelets increases with body size. In small animals (rabbit) the number of wavelets is far below the fibrillation "threshold", whereas for larger sized dogs and for humans this number is at or near the threshold. In the equine atria the relation between WL and available surface area is such that the number of wavelets exceeds the critical number for fibrillation. In still larger animals (elephant and whale) a continuation of this tendency is expected. See text for detailed description.

to 8 hours and in the group of small animals maximally 6 minutes. In another study it was observed that the incidence of atrial fibrillation was much higher in giant than in toy breeds, although in the first group this arrhythmia was associated with a less severe degree of underlying heart disease (Bohn et al. 1971). In man shortlasting periods of atrial fibrillation can be elicited by programmed electrical stimulation, but sustained fibrillation is very unusual in healthy hearts. The relative prolongation

of the wavelength compared to the increase in atrial mass may explain the decreased susceptibility of healthy human hearts to atrial fibrillation in comparison to hearts of large dogs. This may be related to differences in vagal tone, which is usually high in dogs. However, in humans with increased atrial size also an increased vulnerability to atrial fibrillation exists (Henry et al. 1976). Moore et al. (1982) reported periods of induced atrial fibrillation to be comparably short-lasting (<1 minute) in calves and mature goats with similar atrial masses, whereas in full-grown cows these episodes lasted from 90 minutes to several weeks. In equine atria the estimated maximal number of wavelets exceeds the critical number for atrial fibrillation (figure 7.3). Indeed there is some evidence that atrial fibrillation can be present for a long time in otherwise normal horses (Glendinning 1965, Holmes et al. 1969, Deegen 1971). There are several reports on winning racehorses which suddenly started to perform poorly because of atrial fibrillation (Deegen et al. 1976, Rose et al. 1977a, 1977b, Rivard 1977). Treatment with quinidine successfully restored sinus rhythm and long-term performance in these animals. Obviously in horses the balance between wavelength and atrial mass is such that fibrillation, once started, is easily maintained. To our knowledge no research has been conducted on the occurrence of atrial fibrillation in elephants or whales. However, it would not be surprising if this arrhythmia, once induced, would be sustained in normal hearts of these species.

Clinical significance of the wavelength.

Although the mechanisms involved in the genesis of "physiological" atrial arrhythmias in the healthy canine heart are probably not identical to those which cause flutter and fibrillation in the diseased human atrium, most investigators agree that intra-atrial reentry is also responsible for the majority of human atrial arrhythmias (Puech et al. 1970, Wellens 1971, Waldo et al. 1977, Wells et al. 1979, Watson et al. 1980, Inoue et al. 1981, Disertori et al. 1983, Klein et al. 1986). However, the functional or structural abnormalities involved probably alter the susceptibility to these arrhythmias. Thus, depolarization of the cell membrane and slow response action potentials, which may lead to slow conduction, have been

found in atrial fibers from patients with a history of atrial arrhythmias (Hordof et al. 1976, Ten Eick et al. 1979, Mary-Rabine et al. 1983). Moreover, electrical uncoupling of side-to-side fiber connections with increasing age enhances atrial anisotropy (Spach et al. 1986). Together with the development of collagenous septa at older age (Spach et al. 1986), this will promote the occurrence of reentry in the human atria.

In the case of human flutter a number of reports points to the existence of a reentrant circuit with an excitable gap, located in the right atrium (Watson et al. 1980, Inoue et al. 1981, Disertori et al. 1983, Klein et al. 1986). Furthermore, in some studies an area of slow conduction near the orifices of the inferior vena cava and the coronary sinus has been shown to be an essential part of the circuit (Puech et al. 1970, Klein et al. 1986). If such an area of slow conduction extends to anatomical obstacles like the caval or tricuspid orifices, it will favour the occurrence of reentry around these structures. The size of the excitable gap in the resulting circuit will depend on the dimension of the depressed area and the degree of depressed conduction. The larger the excitable gap, the greater the stability of the atrial flutter. Because the size of the excitable gap is equal to the difference between the length of the circuitous pathway and the wavelength, it can theoretically be expected that a prolongation of the wavelength may close the gap and will lead to interruption of the flutter. Administration of a drug which increases the wavelength to that extent might be an appropriate therapy. However, because in diseased hearts the wavelength may be inhomogeneous along the reentrant pathway and the actions of anti-arrhythmic agents may vary at different sites, the response to treatment with wavelength prolonging drugs may be variable and differ from the effects in normal hearts.

Abnormalities in atrial electrophysiology and structure are probably also important in the development of atrial fibrillation. Shortened atrial refractoriness has been associated with a higher vulnerability to fibrillation (Michelucci et al. 1981, Attuel et al. 1982, Olsson et al. 1982). Furthermore, membrane potential abnormalities which will lead to impaired conduction have been found in atrial fibers of patients with chronic atrial fibrillation (Hordof et al. 1976, Rosen et al. 1982). Also extensive degenerative changes are present in atria of such patients (Davies et al. 1972). If atrial fibrillation is based on multiple wandering wavelets which travel

randomly through the myocardium (Moe et al. 1959), it is clear that the above mentioned factors will promote its occurrence. A short refractory period and impaired conduction shorten the wavelength of the impulse, thereby increasing the possible number of wavelets. Enlarged atria, often present in patients with atrial fibrillation, can accommodate even more wavelets, thereby attributing to the stability of the fibrillatory process. Fibrotic, non-excitabile areas will further promote the process because of a high degree of fragmentation of passing wavefronts. Chronic atrial fibrillation is often preceded by episodes of paroxysmal atrial fibrillation (Godtfredsen 1982). The transition from paroxysmal to chronic fibrillation may be due to a further progression of an underlying etiological process. However, there are also some indications that atrial fibrillation per se may cause changes in the myocardium which enhance its irreversibility (Salmon et al. 1985). Pathological studies showed significantly more degenerative atrial changes in long-term than in short-term atrial fibrillation (Davies et al. 1972). The reported high oxygen consumption during atrial fibrillation may explain this phenomenon by creating relative ischemia, which may eventually result in progressive fibrosis (White et al. 1982).

Treatment of atrial fibrillation could be focussed on modification of any of the factors involved. Atrial size and degenerative changes can be reduced surgically, but are difficult to influence by drugs. Therefore, pharmacological prolongation of the wavelength seems a rational basis for therapy and is expected to be most successful in paroxysmal atrial fibrillation. Class III drugs, which in our study were powerful wavelength prolonging agents, have proved to be very effective in treating atrial flutter and fibrillation, even in cases which did not respond to other agents (Rosenbaum et al. 1976, Rowland et al. 1982). In patients in which a class III agent (amiodarone) did not prolong atrial refractoriness, it also failed to prevent recurrences of paroxysmal atrial flutter and fibrillation (Buxton et al. 1985).

It should be noted that apart from wavelength prolongation also the prevention of other precipitating factors can be helpful in the treatment of reentrant arrhythmias. Without a premature depolarization, a reentrant circuit cannot be set up. Thus agents which reduce atrial ectopy, like the beta-adrenergic blocking drug propranolol, have been shown effective in preventing atrial fibrillation in some situations (Fuller et al. 1979,

Stephenson et al. 1980). However, propranolol proved unsuccessful in maintaining sinus rhythm after electroconversion of atrial fibrillation (Tsolakas et al. 1964, Szekely et al. 1970). Holter monitoring may identify patients which are likely to benefit from beta-blocking agents. If the recordings show frequent atrial premature beats, these drugs can be effective in preventing atrial fibrillation for some time (Coumel et al. 1983). Also a decrease in spatial dispersion of refractoriness or heterogeneity in conduction properties may be expected to reduce the occurrence of reentry.

In conclusion, we think that the relationship between the length of the atrial excitation wave and the occurrence of atrial arrhythmias as found in our study, is applicable to the human heart. To evaluate the usefulness of the wavelength as a guide to treat clinical reentrant arrhythmias, catheters should be developed with which atrial refractoriness and conduction velocity can be measured simultaneously. Mapping of atrial excitation during cardiac surgery could open ways to study the relative importance of wavelength and spatial inhomogeneity in the occurrence of human atrial tachy-arrhythmias.

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SUMMARY

The purpose of the study presented in this thesis was to evaluate the usefulness of the wavelength of the atrial impulse as an index of the vulnerability to atrial tachy-arrhythmias. Reentry forms the pathophysiological basis of the far majority of these arrhythmias. Chapter I discusses the factors which affect the occurrence of reentry; they are described in short here. The wavelength of the impulse (the product of refractory period and conduction velocity) determines the minimal size of a reentrant circuit. Therefore, the size of an area of conduction block required to set up a reentrant circuit is proportional to the wavelength. When the wavelength of a premature impulse is long, a large area of conduction block is needed to make the impulse reenter. On the other hand, when the wavelength is short small areas of block may suffice for the initiation of reentrant circuits. Since conduction block is more likely to occur in small areas than in a large portion of the myocardium, the inducibility of reentrant arrhythmias seems to be directly related to the length of the cardiac impulse. The wavelength is also thought to play a major role in the occurrence of atrial fibrillation. This arrhythmia is based on the simultaneous existence of multiple wavefronts which randomly reenter and wander chaotically through the atrium. A short wavelength will highly favour the occurrence of fibrillation, because the resulting small circuit size allows the existence of more circuits in a given tissue mass, thereby decreasing the chance of their simultaneous extinction.

We tested the hypothesis that the wavelength of the impulse is an important determinant for the initiation of atrial arrhythmias in a chronically instrumented, conscious dog model (see chapter II). Electrodes were implanted on the atria, with which refractory period (RP), conduction velocity (CV) and wavelength (WL) could be simultaneously measured at four different atrial sites (the right and left part of Bachmann's bundle and the right and left atrial free wall). This animal model offers the opportunity to directly correlate changes in the measured electrophysiological variables to the inducibility of various atrial tachy-arrhythmias.

We studied the effects of several interventions clinically known to affect the vulnerability to atrial arrhythmias. For example, during programmed electrical stimulation of the heart, atrial arrhythmias can

often be induced by rapid pacing or early premature beats. In chapter III we report that these changes in rate and rhythm caused a decrease of both RP and CV, resulting in a shortening of the wavelength from 46% to 55%. Early premature beats often elicited atrial tachy-arrhythmias. Three different types of arrhythmias were distinguished: 1. rapid repetitive responses (RRR), 2. atrial flutter and 3. atrial fibrillation. To determine which of the three variables (RP, CV and WL) gives the best indication for the vulnerability to these arrhythmias, we investigated the effects of several interventions on these parameters and the related occurrence of RRR, atrial flutter and atrial fibrillation.

One of the factors studied was a variation in autonomic tone (chapter IV). High vagal activity resulted in a marked decrease of both refractory period and wavelength, and was associated with a strong proneness to atrial fibrillation. On the other hand, blockade or attenuation of parasympathetic influence by atropine or treadmill exercise prolonged the refractory period and wavelength, and often coincided with interruption or prevention of atrial fibrillation. Vagal tone also affected spatial differences in refractory period. Spatial dispersion of refractoriness was highest during total autonomic blockade and lowest during a physiologically high vagal tone, due to a stronger vagal influence on areas with a long intrinsic RP (right atrium). In contrast to these marked effects of parasympathetic influence, variation in sympathetic tone caused only minor changes in all variables.

Furthermore, the actions of four cardiac drugs (propafenone, lidocaine, quinidine, d-sotalol) were studied (chapter V). These drugs all profoundly increased the refractory period. However, because of their different action on the conduction velocity, also their effect on the wavelength varied strongly. Both propafenone and lidocaine depressed intra-atrial conduction to such extent that their prolonging effect on refractoriness was counter-balanced, resulting in an unchanged wavelength. This absence of effect on the atrial wavelength was associated with an unchanged vulnerability to atrial tachy-arrhythmias. The two other drugs which lengthened RP, quinidine and d-sotalol, exhibited much less or no depressant effect on CV and therefore strongly prolonged the wavelength. Both drugs featured powerful anti-arrhythmic properties. The last cardioactive agent tested, ouabain, caused a small reduction of the atrial wavelength and exhibited no anti-arrhythmic properties.

In chapter VI we describe the results of a statistical method (discriminant analysis), which we used to determine which of the three electrophysiological properties was the best index for the vulnerability of the atrium to the different arrhythmias. It turned out that it was hazardous to predict atrial susceptibility to these arrhythmias on the basis of the value of either RP or CV (predictive power 48% and 38%, respectively). However, the wavelength turned out to be a more reliable index for the vulnerability to various reentrant atrial arrhythmias (predictive power 75%), with a high sensitivity (88-100%) and specificity (80-96%). Despite wide variations in RP and CV by the various interventions, constant critical wavelength values could be identified for the vulnerability to the different arrhythmias. The critical WL for the initiation of RRR was 12 cm, atrial flutter occurred with a WL shorter than 10 cm, while atrial fibrillation could be induced when the WL was less than 8 cm. It is estimated that at this latter WL the atrial surface area of the dogs used in this study permits the simultaneous existence of about 7 circuits. This number fits with other studies, which indicate that at least 6 wavelets must be synchronously present for fibrillation to be stable. It is speculated that this balance between atrial surface area and wavelength plays a critical role in the well-known difference in susceptibility to atrial fibrillation between mammals of varying size.

Chapter VII gives a general discussion on the correlation between the wavelength and atrial arrhythmias, and the significance of the wavelength for reentrant mechanisms. Furthermore, we discuss the relationship between wavelength, tissue mass and vulnerability to atrial fibrillation, and the clinical significance of the wavelength.

We conclude that the wavelength is a major determinant for the atrial vulnerability to varying reentrant arrhythmias. To test cardiac drugs for anti-arrhythmic properties, their effect on the wavelength should be assessed. Although we did not study other factors, like electrophysiological and structural abnormalities which may also be important in the pathogenesis of clinical atrial arrhythmias, we believe that measurement of the wavelength can be an important tool in the search for effective anti-arrhythmic therapy in patients.

often be induced by rapid pacing or early premature beats. In chapter III we report that these changes in rate and rhythm caused a decrease of both RP and CV, resulting in a shortening of the wavelength from 46% to 55%. Early premature beats often elicited atrial tachy-arrhythmias. Three different types of arrhythmias were distinguished: 1. rapid repetitive responses (RRR), 2. atrial flutter and 3. atrial fibrillation. To determine which of the three variables (RP, CV and WL) gives the best indication for the vulnerability to these arrhythmias, we investigated the effects of several interventions on these parameters and the related occurrence of RRR, atrial flutter and atrial fibrillation.

One of the factors studied was a variation in autonomic tone (chapter IV). High vagal activity resulted in a marked decrease of both refractory period and wavelength, and was associated with a strong proneness to atrial fibrillation. On the other hand, blockade or attenuation of parasympathetic influence by atropine or treadmill exercise prolonged the refractory period and wavelength, and often coincided with interruption or prevention of atrial fibrillation. Vagal tone also affected spatial differences in refractory period. Spatial dispersion of refractoriness was highest during total autonomic blockade and lowest during a physiologically high vagal tone, due to a stronger vagal influence on areas with a long intrinsic RP (right atrium). In contrast to these marked effects of parasympathetic influence, variation in sympathetic tone caused only minor changes in all variables.

Furthermore, the actions of four cardiac drugs (propafenone, lidocaine, quinidine, d-sotalol) were studied (chapter V). These drugs all profoundly increased the refractory period. However, because of their different action on the conduction velocity, also their effect on the wavelength varied strongly. Both propafenone and lidocaine depressed intra-atrial conduction to such extent that their prolonging effect on refractoriness was counter-balanced, resulting in an unchanged wavelength. This absence of effect on the atrial wavelength was associated with an unchanged vulnerability to atrial tachy-arrhythmias. The two other drugs which lengthened RP, quinidine and d-sotalol, exhibited much less or no depressant effect on CV and therefore strongly prolonged the wavelength. Both drugs featured powerful anti-arrhythmic properties. The last cardioactive agent tested, ouabain, caused a small reduction of the atrial wavelength and exhibited no anti-arrhythmic properties.

In chapter VI we describe the results of a statistical method (discriminant analysis), which we used to determine which of the three electrophysiological properties was the best index for the vulnerability of the atrium to the different arrhythmias. It turned out that it was hazardous to predict atrial susceptibility to these arrhythmias on the basis of the value of either RP or CV (predictive power 48% and 38%, respectively). However, the wavelength turned out to be a more reliable index for the vulnerability to various reentrant atrial arrhythmias (predictive power 75%), with a high sensitivity (88-100%) and specificity (80-96%). Despite wide variations in RP and CV by the various interventions, constant critical wavelength values could be identified for the vulnerability to the different arrhythmias. The critical WL for the initiation of RRR was 12 cm, atrial flutter occurred with a WL shorter than 10 cm, while atrial fibrillation could be induced when the WL was less than 8 cm. It is estimated that at this latter WL the atrial surface area of the dogs used in this study permits the simultaneous existence of about 7 circuits. This number fits with other studies, which indicate that at least 6 wavelets must be synchronously present for fibrillation to be stable. It is speculated that this balance between atrial surface area and wavelength plays a critical role in the well-known difference in susceptibility to atrial fibrillation between mammals of varying size.

Chapter VII gives a general discussion on the correlation between the wavelength and atrial arrhythmias, and the significance of the wavelength for reentrant mechanisms. Furthermore, we discuss the relationship between wavelength, tissue mass and vulnerability to atrial fibrillation, and the clinical significance of the wavelength.

We conclude that the wavelength is a major determinant for the atrial vulnerability to varying reentrant arrhythmias. To test cardiac drugs for anti-arrhythmic properties, their effect on the wavelength should be assessed. Although we did not study other factors, like electrophysiological and structural abnormalities which may also be important in the pathogenesis of clinical atrial arrhythmias, we believe that measurement of the wavelength can be an important tool in the search for effective anti-arrhythmic therapy in patients.

SAMENVATTING

Onder normale omstandigheden klopt het hart met een frekwentie van ongeveer 70 slagen per minuut in rust tot 180 slagen per minuut tijdens zware inspanning. De elektrische prikkel die aanzet tot het samentrekken van het hart ontstaat in een klein groepje gespecialiseerde cellen (sinusknoop), gelegen in de hartboezem (atrium). Daarna spreidt de elektrische activatiegolf zich met een dusdanig hoge snelheid uit over de hartboezems dat de hartspiercellen bijna gelijktijdig geprikkeld worden. In de elektrische verbinding tussen de boezems en de kamers van het hart (de AV knoop) ondervindt de activatiegolf enige vertraging, waarna de golf zich ook met hoge snelheid over de kamers (ventrikels) verspreidt. Zodra de grenzen van het hart bereikt zijn dooft de activatiegolf uit. Het gevolg van deze bijna synchrone activatie van de hartspiervezels is een krachtige contractie van het hart. Echter onder bepaalde omstandigheden kan het normale ritme van het hart verstoord worden, waarbij het zowel te langzaam als te snel kan gaan kloppen. Soms kan het ritme zo snel worden dat de normale pompfunctie van het hart sterk achteruitgaat met als gevolg een tekortschietende bloedvoorziening in het lichaam. Behalve te snelle regelmatige ritmes zijn er ook nog ritmestoornissen (arrhythmieën) waarbij de synchronisatie tussen de hartspiervezels verloren is gegaan (fibrilleren). In dat geval trekken de vezels snel en onafhankelijk van elkaar samen waardoor de hartboezems of -kamers als geheel stilstaan en er geen bloed meer wordt uitgepompt. Als dit in de boezems optreedt leidt dit tot een verminderde pompfunctie van het hart en een verhoogde kans op embolieën (bloedpropfen), terwijl kamerfibrilleren plotselinge hartdood tot gevolg heeft.

In een groot aantal gevallen is de oorzaak van deze ritmestoornissen gelegen in het feit dat de activatiegolf niet uitdooft na iedere hartslag, maar gevangen wordt in een cirkelpad waarin de elektrische impuls eindeloos kan ronddraaien (reentry). De tijd tussen twee hartslagen is dan gelijk aan de omlooptijd van deze cirkelbeweging en kan erg kort zijn. Reentry wordt vaak geprovoceerd door een prikkel die vlak na een vorige, nog normale hartslag ergens in het hart ontstaat (extrasystole). Of zo'n extrasystole aanleiding geeft tot reentry hangt af van twee factoren. Ten eerste moet er

in het hart een gebiedje zijn dat de elektrische activatiegolf van de extrasystole niet voortgeleidt (blokgebied), maar waar de golf zodanig omheen gedwongen wordt dat de impuls weer op z'n punt van oorsprong uitkomt. Ten tweede moet op het moment van aankomst van de activatiegolf het punt van oorsprong weer prikkelbaar zijn. Dit laatste hangt af van de tijd die het weefsel nodig heeft om weer prikkelbaar te worden (refractaire periode) en van de geleidingssnelheid van de activatiegolf. Komt de activatiegolf na de omweg om het blokgebied te vroeg aan op z'n punt van oorsprong, door een hoge geleidingssnelheid en/of een lange refractaire periode, dan is dit punt nog niet prikkelbaar en dooft de golf uit. In dat geval treedt dus geen reentry op. Is echter de geleidingssnelheid traag en/of de refractaire periode kort, dan is het oorsprongspunt wel weer prikkelbaar na de rondgang van de activatiegolf om het blokgebied en kan de cirkelbeweging zich eindeloos herhalen. De combinatie van die twee grootheden wordt uitgedrukt in de golflengte van de elektrische impuls (golflengte = geleidingssnelheid x refractaire periode). De golflengte is dus de afstand die de activatiegolf aflegt in de tijd die het hartspierweefsel nodig heeft om weer een nieuwe golf te kunnen voortgeleiden, en is daarom gelijk aan de omtrek van het kleinst mogelijke reentry circuit. Naarmate de golflengte kleiner is zal reentry gemakkelijker kunnen optreden. Is echter de golflengte erg groot, dan is er ook een groot blokgebied nodig om cirkelbeweging mogelijk te maken. Omdat de aanwezigheid van zo'n groot blokgebied erg onwaarschijnlijk is, zal een lange golflengte reentry verhinderen. Aangezien fibrilleren waarschijnlijk berust op het gelijktijdig bestaan van een aantal reentry circuits, is ook voor het al of niet optreden van deze ritmestoornis de golflengte van cruciaal belang. Hoe kleiner de golflengte, en dus de afmetingen van de circuits, hoe meer circuits er simultaan aanwezig kunnen zijn in het hart en hoe kleiner de kans op het gelijktijdig uitdoven van al die circuits.

De hypothese dat een korte golflengte het optreden van arrhythmieën bevordert, terwijl een lange golflengte ze stopt en voorkomt hebben wij getoetst in het atrium van chronisch geïnstrumenteerde, wakkere honden. Daartoe werden electrodes geïmplanteerd op het atrium, waarmee tegelijkertijd de refractaire periode, geleidingssnelheid en golflengte van de impuls gemeten konden worden. Door elektrische prikkels via de elektrodes aan het hart toe te dienen was het mogelijk het hartritme van buitenaf te regelen

en op gewenste tijdstippen extrasystoles op te wekken. Het grote voordeel van dit chronische hondemodel is dat veranderingen in de gemeten grootheden direkt gecorreleerd kunnen worden aan het optreden van ritmestoornissen.

Het effect van een aantal factoren die bij patienten de vatbaarheid voor boezemritmestoornissen beïnvloeden, hebben we in ons model onderzocht. Zo is het bekend dat snelle hartritmes en vroege extrasystoles het optreden van boezemritmestoornissen kunnen bewerkstelligen. Wij vonden dat deze ritmeveranderingen gepaard gingen met een afnemen van zowel refractaire periode als geleidingssnelheid, leidend tot een golflengte verkorting van 46% tot 55%. Door de vroege extrasystoles werden vaak ritmestoornissen opgewekt. Drie verschillende soorten werden onderscheiden: 1. een rijtje spontane extrasystoles, Rapid Repetitive Responses (RRR); 2. boezemfladderen, een zeer snel (350-700 slagen/minuut) maar regelmatig ritme; 3. het nog snellere en volledig onregelmatige boezemfibrilleren. Om uit te zoeken welke van de drie grootheden (refractaire periode, geleidingssnelheid en golflengte) het belangrijkste was voor het al dan niet optreden van de verschillende ritmestoornissen, hebben we hun waarde met behulp van verscheidene interventies gemanipuleerd en vergeleken met de opwekbaarheid van RRR, boezemfladderen of boezemfibrilleren.

Een van de middelen daartoe was het variëren van de activiteit van het autonome zenuwstelsel. Een sterke activiteit van de nervus vagus (de zenuw die in rust de basale functies van het lichaam bestuurt), zoals aanwezig wanneer de hond slaapt, gaf een verkorting van de refractaire periode en de golflengte en viel samen met een gemakkelijke opwekbaarheid en langdurig aanhouden van boezemfibrilleren. Aan de andere kant, vermindering of blokkade van vagale invloed door de hond te wekken en op een tredmolen te laten lopen, gaf een verlenging van refractaire periode en golflengte en resulteerde vaak in het stoppen en voorkomen van atrium-fibrilleren.

Verder werd het effect van vier verschillende geneesmiddelen (propafenon, lidocaine, quinidine en d-sotalol) onderzocht. Al deze middelen veroorzaken een sterke verlenging van de refractaire periode. Maar omdat de invloed op de geleidingssnelheid varieerde, was ook het effect op de golflengte (het produkt van de eerste twee) wisselend. Zowel lidocaine als propafenon vertraagden de geleidingssnelheid van de activatiegolf zo sterk, dat het effect van de refractaire periode verlenging teniet werd gedaan en de golflengte onveranderd bleef. Ook de opwekbaarheid van ritmestoornissen

werd niet beïnvloed door deze stoffen en ze waren meestal niet in staat boezemfladderen of fibrilleren te stoppen. Quinidine en d-sotalol daarentegen hadden veel minder of geen effect op de geleidingssnelheid en daarom resulteerde hun refractaire periode verlengende werking in een sterke vergroting van de golflengte. Beide stoffen waren zeer effectief in zowel het stoppen als het voorkomen van boezemritmestoornissen.

Met behulp van een statistische methode (discriminant analyse) hebben we onderzocht welke van de drie gemeten variabelen nu het beste de vatbaarheid voor de verschillende ritmestoornissen onder al die wisselende omstandigheden aangeeft. Het bleek dat de waarde van noch de refractaire periode noch de geleidingssnelheid een goede indicatie is voor het al of niet opwekbaar zijn van de verschillende arrhythmieën (voorspellende waarde respectievelijk 48% en 38%). De golflengte echter bleek een betrouwbaardere index voor de opwekbaarheid van boezemritmestoornissen te zijn (voorspellende waarde 75%), met een zeer hoge sensitiviteit (88-100%) en specificiteit (80-96%). Onder alle omstandigheden was de golflengte waarbij de verschillende ritmestoornissen ontstonden constant. Deze kritische golflengte bedroeg 12 cm voor RRR, 10 cm voor boezemflutter en 8 cm voor boezemfibrilleren. De verhouding tussen deze laatste golflengte en de beschikbare boezemoppervlakte is zodanig dat ongeveer 7 circuits tegelijk in het atrium aanwezig kunnen zijn. De wisselende verhouding tussen atrium oppervlakte en golflengte verklaart waarschijnlijk de verschillende vatbaarheid voor fibrilleren tussen diersoorten van wisselende grootte. In kleine diersoorten is het maximale aantal circuits en de gevoeligheid voor fibrilleren laag, terwijl voor grote diersoorten het omgekeerde geldt.

De conclusie van deze studie is dat de golflengte een cruciale rol speelt in het al dan niet optreden van boezemritmestoornissen. Een korte golflengte verhoogt hun opwekbaarheid, terwijl een lange golflengte het optreden van deze ritmestoornissen voorkomt. Om de doeltreffendheid van geneesmiddelen voor de behandeling van boezemritmestoornissen te beoordelen, dient daarom het effect van deze middelen op de golflengte onderzocht te worden.

NAWOORD

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