Atrial pacing and experimental atrial fibrillation in equines

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For Fien, Emma and Sofie, who maintain my rhythms
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*List of abbreviations*

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# LIST OF ABBREVIATIONS

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<tr>
<td>AERP</td>
<td>atrial effective refractory period</td>
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<tr>
<td>AF</td>
<td>atrial fibrillation</td>
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<tr>
<td>AFCL</td>
<td>atrial fibrillation cycle length</td>
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<tr>
<td>AV</td>
<td>atrioventricular</td>
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<tr>
<td>CL</td>
<td>cycle length</td>
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<tr>
<td>ECG</td>
<td>electrocardiogram</td>
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<tr>
<td>S1</td>
<td>driving stimulus</td>
</tr>
<tr>
<td>S2</td>
<td>extrastimulus</td>
</tr>
<tr>
<td>SCL</td>
<td>sinus cycle length</td>
</tr>
<tr>
<td>(c)SNRT</td>
<td>(corrected) sinus node recovery time</td>
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<tr>
<td>SR</td>
<td>sinus rhythm</td>
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Diagnosis and treatment of cardiac rhythm disturbances in equines has remained virtually unchanged during the past decades. In human medicine, invasive cardiac testing, using electrical stimulation or ‘pacing’ of the heart, has greatly changed the approach to arrhythmias. Besides diagnostic and therapeutic application, the technique also provides an excellent means to study arrhythmias in animal models.

In addition to the investigation of the applicability of cardiac pacing in equines, this work reports results of basic research on atrial fibrillation, clinically the most important arrhythmia in equines. The study on atrial fibrillation in equines was performed in different pony models making use of the atrial pacing technique.

The thesis is divided into two sections. The first section provides information and results about atrial pacing. It describes the application of temporary and permanent pacing. Section 2 applies atrial pacing to develop a chronic atrial fibrillation model in equines and discusses the consequence of pacing-induced atrial fibrillation in the equine heart.
GENERAL INTRODUCTION
ATRIAL PACING

DESCRIPTION OF CARDIAC PACING

Excitable properties of cardiac cells

Like all living cells, the inside of cardiac cells has a negative electrical charge compared to the outside of cells (-90 mV). The resulting voltage difference is called the transmembrane potential. Due to the excitable properties of cardiac cells, each process reducing the resting transmembrane potential to a critical value or threshold (-65 mV) results in the generation of an action potential. This action potential arises from patterned changes in transmembrane potential due to sequential opening and closing of ion channels. When these stereotypical voltage changes in a single cardiac cell are graphed against time, the result is the action potential (Fig. 1). The action potential starts with a rapid, positively directed change in transmembrane potential, resulting in a voltage spike called depolarisation (phase 0). After this fast depolarisation, a gradual normalization of ion concentrations occurs and the cell repolarises, a process that roughly corresponds to phases 1 through 3 of the action potential. Because a second depolarisation cannot take place until repolarisation occurs, the time from the end of phase 0 to late in phase 3 is called the absolute refractory period of
cardiac tissue. As the cells gradually recover from refractoriness, they become excitable if a pulse of sufficient strength is delivered. The period after the absolute refractory period and before full recovery is called the relative refractory period (Fogoros, 1995; Kay, 1996). Stimulation at the end of the refractory period, can initiate tachyarrhythmias (Fishler and Thakor, 1994; Peters et al., 1994).

For most cardiac cells, after full recovery, the resting phase (the period of time between action potentials, corresponding to phase 4) is quiescent, and there is no net movement of ions across the cell membrane. In some cells, a leakage of ions across the cell membrane causes a gradual increase in transmembrane potential during phase 4, which results in a spontaneous depolarisation, called automaticity. Cells in the sinoatrial node have the fastest phase 4 activity. The sinoatrial node therefore regulates heart rate and is called the natural pacemaker of the heart.

The spontaneously generated electrical impulse from the sinoatrial node stimulates nearby cells to depolarise. Depolarisation of one cardiac cell tends to cause adjacent cells to depolarise. Thus, once a cell is stimulated the wave of depolarisation (the electrical impulse) is propagated across the atrium, cell by cell (Fogoros, 1995). The atrial depolarisation can be recognised on the surface electrocardiogram (ECG) by the P wave. At the atrioventricular node conduction is slowed, which is reflected in the PR interval on the surface electrocardiogram (ECG). Leaving the atrioventricular node, the His bundle and Purkinje fibres rapidly spread the impulse throughout the ventricles. On the surface ECG, the ventricular depolarisation and subsequent repolarisation generate a QRS complex and T wave, respectively.

Besides natural depolarisation due to sinus node activity, cardiac cells can be stimulated artificially by electrical pulses, which is called pacing. The electrical stimulus generally consists of a square current pulse with variable amplitude, duration and interval. Only when the
Electrical current is able to reduce the resting potential of the cardiac cells by a critical amount and within a critical time, a self-regenerating wavefront of action potentials will propagate from the site of stimulation across the cardiac chamber and 'capture' is being achieved (Trautwein, 1975). Not only the amplitude but also the duration of the stimulating current determines whether the threshold for stimulation will be reached. Currents larger in amplitude require a shorter duration to reach threshold and vice versa. The strength-duration curve describes the threshold for stimulation at different pulse widths and amplitudes during the excitable period of the tissue. Pacing during the absolute refractory period will not result in capture. Pacing during the relative refractory period can result in capture if the pulse has a sufficient strength. Caution is warranted, especially during ventricular stimulation, not to stimulate immediately after the end of the refractory period, during the 'vulnerable period', because this can initiate fibrillation (Fishler and Thakor, 1994; Peters et al., 1994). To avoid this problem most pulse generators have the possibility to 'sense' spontaneous electrical activity of the heart through the electrodes. Immediately after sensing a cardiac depolarisation, artificial stimulation is temporarily inhibited to minimise the risk of fibrillation induction.

Successful myocardial stimulation is dependent on (1) a source of the electrical pulse (the pulse generator), (2) a conductor between the source of the electrical pulse and the stimulating electrode (the lead), (3) an electrode for pulse delivery and (4) an area of myocardium that is excitable.

**Pulse generator**

Three basic electronic circuits are essential for the pulse generator (Mond and Sloman, 1990). The timing circuit controls the pacing interval and the output circuit controls the charging and discharging of the impulse. The third major circuit is the sensing circuit, which analyses the electrical signals that return to the pulse generator from the heart via the lead and which is responsible for the recognition of
spontaneous intracardiac electrical signals. This sensing circuit allows the pacemaker to adjust its timing intervals to changes in spontaneous cardiac activity and prevents pacing during the vulnerable period because this could initiate tachyarrhythmias (Fishler and Thakor, 1994; Peters et al., 1994; Hayes and Osborn, 1996).

The pulse generator can deliver pulses of different strength and duration at a desired rate. Different pacing protocols as overdrive pacing, extrastimulus pacing and burst pacing are available to fulfil electrophysiologic studies. During temporary stimulation, an external pulse generator is used for pulse delivery, while for permanent pacing an implantable pacemaker is applied (Fig. 2).

![Figure 2. An implantable pacemaker (1) with an atrial and ventricular lead (2) is shown. Each lead possesses an electrode on the lead-tip (3). The lead can be of the active (3a) or passive (3b) fixation type.](image)

Using radiofrequency signals or pulsed magnetic fields, the pulse generator is capable of both transmitting information to and receiving information from an external programmer (Kay, 1996). Consequently, this telemetric programmability allows changing most functions of the implanted pacemaker non-invasively.

Originally pacemakers were classified with a three-letter identification code according to the site of the pacing electrodes and the mode of pacing: V = ventricle, A = atrium, D = dual, I = inhibited and T = triggered (Mond and Sloman, 1990; Barold and Zipes, 1992; Hayes and Osborn, 1996). The first letter indicates the chamber paced and the second the chamber sensed. Occasionally the letter S is used for the first or second position to indicate that a single-chamber device
is suitable for atrial or ventricular pacing. The third position indicates the response of the pacemaker when a cardiac signal is sensed, i.e. inhibition of pulse delivery (I), triggering of pulse delivery (T) or both (D). For instance, the AAI mode means that atrial pacing and atrial sensing occur and that an atrial stimulus will be inhibited when an atrial signal is sensed. The (lower) heart rate in these models can be chosen and will prevent a rate drop below this value. The major advantage of rate programming is to allow the patient to remain in sinus rhythm rather than in paced rhythm when intermittent bradycardia is present (Hayes and Osborn, 1996).

During 1980 the code was extended to five letters to indicate other complex pacing functions. However, we wish to limit the discussion to the letter R in the fourth position, indicating that the pacemaker has rate modulation, which can be achieved by a build-in sensor. As an example, the DDIR mode indicates that rate adaptive atrial and ventricular pacing occurs provided that no atrial or ventricular signals are sensed. Depending on the kind of pacemaker, sensor activation occurs due to patient physical activity, changes in respiratory rate, changes in QT interval,… Upon stimulation of the sensor, a sensor-driven response in heart rate occurs, better meeting the metabolic demands of the patient. The upper sensor-driven heart rate, which will be gradually achieved after continuous sensor activation, can be programmed. When patient activity stops, sensor stimulation is ceased and the pacing rate will gradually decrease.

**Electrodes**

Using properly positioned electrodes, the atria and/or ventricles can be selectively stimulated. In general, the electrodes can be positioned nearby the heart, on the epicardium or on the endocardium. In man, transcutaneous atrial or ventricular pacing can be performed in emergency situations using relatively high currents (Barold and Zipes, 1992). But this technique can be painful in conscious patients due to stimulation of cutaneous nerves and pacing-induced skeletal muscle
contractions. Transoesophageal atrial pacing implies a markedly lower threshold and can be performed without general anaesthesia or sedation (Tucker and Wilson, 1993; Kantharia and Mookherjee, 1995). The technique is relatively non-invasive and well tolerated. Ventricular capture is inconsistent or often intolerably painful, however, thus seriously limiting the therapeutic and emergent application of the procedure. After a thoracotomy and incision of the pericardium, electrodes can be attached directly on the atrial and/or ventricular epicardium. Resistance for electrical stimulation is low and thresholds are more easily reached. Because even low currents remain effective to provoke myocardial excitation, stimulation itself is not painful making this technique suitable for pacing in the conscious patient. The necessity of a thoracotomy, however, limits the technique to temporary pacing during cardiac surgery or to permanent pacing with an implanted device (Amsel and Walter, 1992). In humans and small animals, the most widely used approach for cardiac pacing is transvenous endocardial pacing, where a lead or catheter, with electrodes on its tip, is introduced through a vein and advanced into the atrial or ventricular cavity. Correct positioning of the electrode can be guided by fluoroscopy, echocardiography, intracavitary electrogram morphology and application of testing stimuli. When the lead is connected to an electrocardiographic device, simultaneous recording of the intracavitary electrogram and the surface ECG can reveal the position of the electrode. After introduction of the electrode into the vein, the 'intravenous' electrogram will be characterised by absent or minimal deflections. When the electrode enters the right atrium or the right ventricle, the largest intra-cardiac electrogram deflections will coincide with, respectively, the P waves or QRS complexes on the surface ECG. When the lead tip is assumed to be located in the desired chamber, testing stimuli with a sufficient strength can be applied to confirm its position: intra-atrial or intraventricular stimulation will produce a P wave or QRS complex on the surface ECG, respectively.
To achieve permanent pacing, two types of transvenous leads have been developed to preserve endocardial contact. Leads with an active fixation invade the endocardium with screws or small jaws, while leads with a passive fixation promote fixation to the endocardium by indirect means. The latter can be obtained by little tines or fins to enhance entanglement in myocardial trabeculae (Mond and Sloman, 1990; Barold and Zipes, 1992). In general, the ventricular lead can be of the passive or active fixation type, while the atrial lead should include an active fixation mechanism to remain in a stable position.
CARDIAC PACING IN HUMAN MEDICINE

Therapeutic pacing

Permanent pacing

Although pacemaker implantation can be utilized to prevent induction of certain tachyarrhythmias (Osborn, 1996), the major therapeutic indications for permanent cardiac pacing are bradyarrhythmias due to third-degree or second-degree AV block, sinus node dysfunction or neurocardiogenic syncope (Barold and Zipes, 1992; Ross and Mandel, 1995; Ellenbogen and Peters, 1996; Hayes and Osborn, 1996). Formerly, pacemaker implantation was performed with epicardial lead placement and therefore required major surgery. A considerable evolution during the past decades, however, has greatly simplified the implantation procedure. Today, virtually all leads are transvenously inserted, making cardiac pacing a relatively simple and safe method that is widely used in human medicine (Holmes and Hayes David, 1990). Because major surgery is avoided, the transvenous approach can be performed without general anaesthesia (Barold and Zipes, 1992).

The pacing system consists of a pacemaker and 1 or 2 leads to perform single chamber (atrial or ventricular) or dual chamber pacing. Recent pacemakers are equipped with a build-in sensor that detects patient activity, thus providing an exercise-dependent rate response.

Temporary pacing

Temporary cardiac pacing can be accomplished transcutaneously, via the oesophagus, transvenously and epicardially. Temporary cardiac pacing serves as a lifesaving therapy in the acute management of medically refractory bradyarrhythmias (Wood and Ellenbogen, 1996). Temporary pacing is also indicated prophylactically
in patients with a high risk of developing high-degree AV block, severe sinus node dysfunction, or asystole in acute myocardial infarction, after cardiac surgery, during cardiac catheterisation, and occasionally before implantation or replacement of a permanent pacemaker (Barold and Zipes, 1992). Rapid temporary pacing can be used to terminate atrial flutter, AV reentry tachycardia or AV nodal reentry tachycardia, and sustained ventricular tachycardia (Barold and Zipes, 1992; Kantharia and Mookherjee, 1995; Ross and Mandel, 1995; Osborn, 1996). Finally, temporary pacing can be applied to prevent bradycardia-dependent ventricular tachycardia (torsade de pointes).

**Non-therapeutic pacing: the electrophysiological study**

The approach to the diagnosis of cardiac rhythm disturbances starts with a detailed history, clinical examination of the patient and an ECG recording. Further examinations include exercise testing and long-term ECG recordings. However, during the past decades, invasive electrophysiologic studies have proven to be of great benefit in the management of cardiac arrhythmias.

To perform an electrophysiologic study, in general, one or more temporary pacing catheters have to be transvenously introduced into the cardiac chamber. Fluoroscopy and intracavitary electrogram recordings are applied for proper catheter positioning (Ross and Mandel, 1995). Although two simple things are being done, i.e. pacing and recording from localized areas within the heart, complex programmed electrical stimulation protocols are often used. These pacing protocols apply two general types of programmed electrical stimulation: incremental pacing and extrastimulus pacing. With incremental pacing (or burst pacing) the heart is stimulated at a constant rhythm in excess of the spontaneous heart rate. The extrastimulus technique consists of introducing one or more premature impulses, each at its own specific coupling interval.
During an electrophysiological study, automaticity and conductivity of the sinoatrial (SA) node, and conductivity and refractoriness of the atrioventricular (AV) node and His-Purkinje system are assessed. By rapid atrial pacing, the automaticity and conductivity of the SA node can be assessed. Rapid atrial pacing depolarises the SA node faster than it can be depolarised by its intrinsic automaticity. When the overdrive pacing is abruptly stopped there is often a relatively long pause before the SA node recovers and begins depolarising spontaneously again. A diseased SA node tends to have a grossly prolonged recovery time (Zipes, 1992; Fogoros, 1995).

By delivering a properly timed extrastimulus with a short coupling interval, myocardial refractoriness can be determined. If the coupling interval between the last paced or spontaneous beat and the extrastimulus is too short, the stimulus will fall in the refractory period and no depolarisation will be initiated. However, a stimulus given after the refractory period will cause an extrasystole or even initiate tachycardia or fibrillation. The longest coupling interval not resulting in a propagated cardiac depolarisation indicates the effective refractory period of that tissue (Fogoros, 1995; Ross and Mandel, 1995).

Initiation of tachyarrhythmias is a potential hazard of cardiac pacing. However, initiation of these tachyarrhythmias is often attempted to assess the existence of an appropriate anatomic substrate to encompass a reentrant circuit. Programmed electrical stimulation also allows to terminate many reentrant arrhythmias. Consequently, the electrophysiologic study has become vitally important in the evaluation and treatment of reentrant tachyarrhythmias.

Complications that can be encountered with temporary or permanent pacing include vascular thrombosis, embolisation, infection, lead fracture, cardiac perforation or failure of the pacing system (Brinker and Midei, 1996).
CARDIAC PACING IN EQUINE MEDICINE

Therapeutic pacing

Permanent pacing

In 1973, Berg et al. described the permanent implantation of a ventricular pacemaker in a young donkey with third-degree AV block. A thoracotomy was performed under general anaesthesia and an epicardial electrode was implanted on the left ventricle. The pacemaker was inserted subcutaneously caudal to the left elbow. After 6 weeks, however, capture was lost, whereby pacemaker function could not be restored. The donkey died 3 weeks later. In 1979, Brown reported a horse with third-degree AV block. In an attempt to implant a permanent pacemaker during general anaesthesia, the horse developed ventricular fibrillation and died. Five years later, Le Nihouannen et al. (1984a; 1984b) reported two techniques for experimental pacemaker implantation in equines. Under general anaesthesia, they performed a thoracotomy in a pony to place 2 epicardial electrodes on the left ventricle and subsequently implanted a pacemaker underneath the ascendant pectoral muscle. During a 60-day follow-up period, the horse could be successfully paced. In another horse, an implantable passive fixation lead was transvenously inserted through the jugular vein into the right ventricle under radioscopic control. This procedure was performed in the standing, sedated animal. Implantation of a pacemaker was not reported in this animal. In 1986, Reef et al. performed a single chamber (ventricular) pacemaker implantation in a horse with third-degree AV block. Under general anaesthesia, a passive fixation lead was inserted in the jugular vein and placed in the right ventricular apex under ultrasonographic control. The pacemaker pocket was created dorsal to the jugular vein. The pacemaker was programmed to maintain a ventricular rate of 45/min. However, due to this fixed heart rate, the horses’ performance was limited. Sixteen months after the implantation, a second lead with
active fixation was implanted in the right atrium under general anaesthesia and the pacemaker was updated to a dual chamber model, allowing AV sequential pacing of the ventricles. This type of pacemaker delivered a ventricular stimulus each time an atrial depolarisation was sensed. Because in this horse with third degree AV block the sinus node still functioned properly, AV sequential pacing allowed the ventricular rate to ‘follow’ the atrial rate, resulting in a physiologic rate response to exercise or stress. About 3 years after the initial implantation, this horse suddenly died. At post mortem, extensive thrombi, a suppurative endocarditis and suspicion of a terminal bacteraemia were present (Hamir and Reef, 1989). In 1993, Pibarot et al. described the implantation of a dual chamber pacemaker in a donkey with complete AV block. Epicardial electrodes were implanted on the left atrium and the left ventricle under general anaesthesia. Due to a high post-operative ventricular threshold, the dual chamber system had to be programmed to a single chamber (ventricular) pacing mode to preserve battery life. After a 12-month follow-up period, successful ventricular pacing could still be achieved.

**Temporary pacing**

The first report about temporary pacing in a horse was published in 1967 by Taylor and Mero. They reported transvenous endocardial ventricular pacing using an external pacemaker in a foal with third-degree AV block. An electrode was introduced through the jugular vein and right ventricular pacing was applied during 45 minutes. A similar technique was used in some of the above-described animals with 3rd degree AV block to avoid Adams-Stokes attacks prior to the permanent implantation of pacemaker (Brown, 1979; Reef et al., 1986; Pibarot et al., 1993).
Non-therapeutic pacing

**Permanent pacing**

With a pacemaker, the effect of a sustained tachycardia can be imitated, arrhythmias can be generated and their inducibility verified, and furthermore, electrophysiologic measurements e.g. determination of the refractory period, can be made. This allows studying the pathophysiology of acute or long-term arrhythmias and developing different therapeutic strategies. Pacemaker implantation has been used in many animal-based research protocols using dogs (Allworth et al., 1995; Morillo et al., 1995; Elvan et al., 1996; Yue et al., 1997), goats (Wijffels et al., 1995), sheep (Willems et al., 2000) or pigs (Qi et al., 2000). However, no literature data were found concerning permanent pacemaker implantation in equines for diagnostic or investigational purposes.

**Temporary pacing**

In 1977, O'Callaghan mentioned that, by analogy with human medicine, cardiac electro-stimulation techniques could be useful to investigate sinus node function, refractory periods, conduction times, vulnerability of the atria for fibrillation and the effect of cardiac drugs on conduction and refractory period in equines. Although the author stated that pacing techniques were under investigation in their institute, to the best of our knowledge, results could not be found in literature.

As rapid overdrive pacing or extrastimulus pacing is able to induce atrial or ventricular fibrillation or flutter (Brignole et al., 1986; Fogoros, 1995), the technique is suitable to study these arrhythmias. In 1975, in a preliminary note, Senta et al. reported that, using temporary atrial pacing, short-term periods of AF could be induced in healthy horses. The bouts of AF persisted from 5 seconds to more than an hour and allowed them to study the effect of short-term AF on the cardiac output (Kubo et al., 1975). In 1978, Senta and Kubo applied rapid atrial
pacing and extrastimulus pacing to determine the ‘vulnerable period’ for AF induction, which turned out to range from 0.14 to 0.42 seconds. Moore and Spear (1987) induced AF by rapid atrial pacing (30 stimuli per second) during 30 seconds in different animal species including mules and mature horses to study the duration of the induced AF episode and the ventricular response during AF.

In equines, ventricular fibrillation has been induced in order to investigate different ventricular defibrillation techniques. This was performed by rapid pacing with stimuli applied to the ventricular surface during thoracotomy (Witzel et al., 1968; Geddes et al., 1974) or to the ventricular endocardium using a temporary pacing catheter (Tacker et al., 1973; Tacker et al., 1975),

Yamaya et al. (1997a; 1997b) applied atrial overdrive pacing to investigate AV conductive function in horses.
ATRIAL FIBRILLATION

In human medicine, acute and chronic AF have been described extensively. The latter form is further subdivided in paroxysmal, persistent and permanent AF. Paroxysmal AF includes cases in which episodes of AF terminate spontaneously without any therapy. If AF persists until a successful treatment is initiated it is called persistent AF. When AF continues despite treatment, permanent AF is said to be present (Gallagher and Camm, 1998; Allessie et al., 2001).

GENERAL ELECTROPHYSIOLOGICAL CONSIDERATIONS

The reentry phenomenon

Under normal circumstances, cardiac activation starts with a depolarisation from the sinus node. This impulse spreads throughout the atria, generating a P wave on the surface ECG. After a slow conduction through the AV node, corresponding with the P-R segment, the impulse conducts over the His-Purkinje network to depolarise the ventricles (Petch, 1986). At the start of cardiac depolarisation, each cell becomes activated in turn and the cardiac impulse dies out when all fibres have been discharged and are completely refractory. During this absolute refractory period, the cardiac impulse has “no place to go”. It must be extinguished and restarted by the next sinus impulse. If, however a group of fibres not activated during the initial wave of depolarisation recovers excitability in time to be discharged before the impulse dies out, they may serve as a link to reexcite areas that were just discharged and have now recovered from the initial depolarisation. Such a process is called reentry, reentrant excitation or circus movement (Zipes, 1992).
Reentry requires a pathway with unidirectional block and slow conduction and in order to continue, the anatomical length of the circuit travelled should equal or exceed the reentrant wavelength. The latter is equal to the mean conduction velocity of the impulse multiplied by the longest refractory period of the elements in the circuit. Conditions that depress conduction velocity or abbreviate the refractory period will promote the development of reentry.

Already around 1960, Moe and co-workers (Moe et al., 1959; Moe, 1962; Moe et al., 1964) introduced the hypothesis that atrial fibrillation consists of multiple reentry waves wandering around in the atria. The more wavelets present at the same time, the smaller the probability that they die out simultaneously and the smaller the chance AF terminates. Therefore large atria are more likely to maintain AF. A decreased conduction velocity and a decreased refractory period shorten the wavelength and allow more wavelets to coexist in the atria, thereby favouring AF perpetuation (Zipes, 1997). In addition of this pathological triad of chronic fibrillation (atrial dilatation, shortened refractoriness and depressed conduction), also increased heterogeneity in intra-atrial conduction and spatial dispersion in recovery of excitability may be of crucial importance (Wijffels et al., 1995; Allessie, 1998).

**Initiation and perpetuation of AF**

In man, diverse triggers can initiate AF especially if a vulnerable substrate is present. These triggers include sympathetic or parasympathetic stimulation, bradycardia, atrial premature beats or tachycardia, and acute atrial stretch (Allessie et al., 2001). Also ectopic foci in sleeves of atrial tissue within the pulmonary veins or vena cava junctions can initiate AF (Haissaguerre et al., 1998; Tsai et al., 2000). In experimental animal models, AF induction can be triggered by rapid atrial pacing (Morillo et al., 1995; Wijffels et al., 1995; Elvan et al., 1996). Moreover, it appeared that AF itself produced changes in the
electrophysiological properties of the myocardium that further promoted the AF perpetuation.

From human medicine, it is known that any process that infiltrates, irritates, inflames, scars, or stretches the atria may predispose them to fibrillate (Gallagher and Camm, 1998). This entails that AF often is the result of underlying disease. The most important predisposing conditions in human medicine include myocardial infiltration or inflammation (neoplasia, pericarditis, myocarditis), atrial scars, atrial stretch or hypertrophy (valvular lesions, pulmonary hypertension, congenital heart disease), myocardial degeneration and hormonal, neural or metabolic imbalances (thyrotoxicosis, electrolyte disturbances, autonomic status, systemic infection) (Gallagher and Camm, 1998). Besides, AF can present without evidence of other cardiac or systemic disease known to promote AF, and since 1954 this is usually described by the term lone AF (Evans and Swann, 1954) or idiopathic AF.

**ATRIAL FIBRILLATION IN EQUINES**

About a century ago, irregularity of the pulse was termed *pulsus irregularis perpetuus* (Hering, 1908). The rapid but hemodynamically ineffectual movement of atrium or ventricle, inducible by electrical stimulation, was known as ‘delerium cordis’ (Hoffa and Ludwig, 1850), ‘frémissement fibrillaire’ (Vulpian, 1874) and ‘undulatory movement’ (Gaskell, 1900). In 1909, Sir Thomas Lewis merged the different concepts under the term auricular fibrillation. But only in 1911, Thomas Lewis was the first to demonstrate the link between an irregular heart rate and atrial fibrillation. From *in situ* studies in horses he concluded that the ‘tumultuous action of the heart’, i.e. the irregularity which occurs in the action of the ventricles, was in reality the outcome of fibrillation of the auricles. As such, research in equines contributed significantly to the early understanding of AF (Moore and Spear, 1987).
Atrial fibrillation (AF) is the most common, clinically significant, pathological arrhythmia in the horse (Bertone and Wingfield, 1987; Manohar and Smetzer, 1992; Reef et al., 1995). The prevalence of AF in horses is described to range from 0.23 to 5.3% (Holmes et al., 1969; Deegen, 1971; Else and Holmes, 1971; Deem and Fregin, 1982). All breeds can be affected but AF more frequently occurs in large breed horses and is virtually never seen in ponies (Holmes et al., 1969; Else and Holmes, 1971; Deem and Fregin, 1982; Reef et al., 1988). Some authors suggest that males are more frequently affected (Holmes et al., 1969; Else and Holmes, 1971; Deem and Fregin, 1982; Reef et al., 1988; Reef et al., 1995), while others didn’t find a gender predilection. AF occurs at all ages and is even encountered in neonatal foals (Machida et al., 1989; Yamamoto et al., 1992).

**Etiology**

Horses with AF may be classified into 2 groups: one in which existence of underlying disease is obvious (Else and Holmes, 1971) and the other in which underlying disease is not apparent, so-called lone fibrillators (Holmes et al., 1986). Horses in the latter group tend to be young and generally are referred for examination because of exercise intolerance (Deem and Fregin, 1982).

Underlying diseases that may predispose horses to AF include electrolyte imbalances (Holmes et al., 1986), respiratory disease (Glazier and Kavanagh, 1977; Deegen, 1986; Gelberg et al., 1991), gastrointestinal disorders (Reef et al., 1988) and especially heart disease. Horses with cardiac failure commonly develop AF (Deem and Fregin, 1982; Belgrave, 1990; Taylor et al., 1991; Seahorn and Hormanski, 1993; Blissett, 1999). Animals with atrial dilatation are more predisposed to the development of AF (Else and Holmes, 1971; Bertone et al., 1987; Detweiler, 1989; Stadler et al., 1994) and this most commonly occurs secondary to mitral or tricuspid valvular regurgitation (Holmes et al., 1969; Else and Holmes, 1971; Kiryu et al., 1974; Deem and Fregin, 1982; Morris and Fregin, 1982; Deegen,
Increased atrial fibrosis has been reported in AF affected horses (Else and Holmes, 1971; Gerber et al., 1972; Button et al., 1980; Muylle et al., 1981; Nuytten et al., 1981; Deegen, 1986). The cause of this fibrosis was thought to be related to local circulatory disturbances caused by arteriolar wall thickening (Amada and Kiryu, 1987) and to over-exertion and strain (Else and Holmes, 1971). From human medicine we know that atrial myocardial damage can be the source of atrial premature depolarisations and might increase the chance for AF initiation and perpetuation (Allessie et al., 2001). However, atrial fibrosis is also commonly found in horses in normal sinus rhythm (Else and Holmes, 1971; Bertone and Wingfield, 1987).

Besides AF secondary to other disease, horses most frequently present lone AF (Amada et al., 1974; Rose and Davis, 1977b; Deem and Fregin, 1982; Reef et al., 1988; Detweiler, 1989; Stewart et al., 1990; Collatos, 1995). Lone AF is said to be present if no other abnormalities are found on clinical and biochemical examination, ECG, and cardiac ultrasound. Often these animals respond better to medical antiarrhythmic treatment. Up to 87.5% of these animals may be treated successfully and many return to their previous level of performance (Reef et al., 1988). Although some of these horses might present the aforementioned myocardial lesions that remain undiagnosed, lone AF is still said to be present because high-level performances can be achieved after treatment.

The paroxysmal form of AF is occasionally encountered, usually in the absence of underlying cardiac disease. Occurrence of paroxysmal AF has been related to the presence of atrial premature depolarisations, increased intra-atrial pressure and increased atrial strain, myocardial ischemia, electrolyte disturbances such as potassium depletion (which might be related to administration of diuretics in racehorses), and changes in autonomic tone (Donald and Elliott, 1948; Detweiler, 1952; Glazier et al., 1959; Else and Holmes,
1971; Machida et al., 1989; Gallagher and Camm, 1998). Possibly due to a high vagal tone, paroxysmal AF has also been described in neonatal foals (Machida et al., 1989; Yamamoto et al., 1992) and during eye enucleation in a horse (Gasthuys et al., 1988).

**Hemodynamics**

During atrial fibrillation, multiple reentry wavelets meander around in the atria causing contraction of individual areas of myocardium rather than a synchronous atrial contraction. Due to the loss of concerted atrial contraction, filling of the ventricles occurs passively and is attributable mainly to the flow and pressure gradient transmitted from the venous and pulmonary capillary beds (Holmes et al., 1986; Bertone and Wingfield, 1987). As a result, ventricular preload is reduced and stroke volume decreases (Abildskov et al., 1971; Kubo et al., 1975; Deegen and Bntenkotter, 1976; Wingfield et al., 1980; Deem and Fregin, 1982; Miller and Holmes, 1984; Muir and McGuirk, 1984; Deegen, 1986; Betsch, 1991; Marr et al., 1994; Marr et al., 1995). Atrial asystole prevents presystolic atrioventricular (AV) valve closure, leading to AV valve regurgitation. Ventricular performance in AF can vary strikingly because of the influence of variations in beat-to-beat intervals on the contractile performance (Manohar and Smetzer, 1992). A pressure increase in right and left atrium is often present which might explain the occurrence of epistaxis, ventral oedema or lung oedema in AF horses (Else and Holmes, 1971; Muir and McGuirk, 1984; Bonagura, 1985; Amada and Kiryu, 1987; Bertone and Wingfield, 1987; Stadler et al., 1994).

At rest, the aforementioned alterations are of little importance because most of the ventricular filling occurs early in diastole during the rapid ventricular filling phase and because reflex mechanisms act to maintain an adequate circulation if no other abnormalities are present (Oldham et al., 1967). As a result of compensatory mechanisms and because of the high vagal tone in horses reducing AV conduction, resting heart rate in horses without underlying heart
disease remains normal (Roos, 1924; Deem and Fregin, 1982; Deegen, 1986).

During exercise, however, when tachycardia abbreviates ventricular diastole, booster pump function of the atria becomes very important in achieving adequate ventricular filling to maintain appropriate stroke volume (Miller and Holmes, 1984; Manohar and Smetzer, 1992). Moreover, AF horses present an abnormally rapid heart rate during excitement or exercise, further hampering cardiac performance (Fregin, 1971; Deegen and Buntenkotter, 1976; Steel et al., 1976; Maier-Bock and Ehrlein, 1978; Deegen, 1986). Accordingly, exercise intolerance is the most important complaint in AF affected horses.

**Symptoms**

Symptoms of AF largely vary according to the degree of underlying disease and the exercise load demanded from the patient. In breeding or pleasure horses, AF is usually an incidental finding as physical strain is too small to elicit complaints about performance. Obvious symptoms in this group of patients are usually indicative of concomitant congestive heart failure. Performance horses usually present exercise intolerance (Mitten, 1996). Increased left and right atrial pressures may result in lung oedema, epistaxis and ventral oedema. Due to the decreased ventricular function, the abnormal pressures, the lung oedema and possibly the occurrence of ventricular tachyarrhythmias, horses may show weakness, incoordination, collapse or sudden death (Donald and Elliott, 1948; Deem and Fregin, 1982; Amada and Kiryu, 1987; Bertone and Wingfield, 1987).

Occasionally, paroxysmal AF is encountered in racehorses, causing a sudden decrease in performance (Amada and Kurita, 1975; Rose and Davis, 1977a; Holmes et al., 1986; Miller et al., 1992; Hiraga and Kubo, 1999). In these animals AF has been suggested to occur without underlying heart disease.
**Diagnosis and treatment**

Patient history most frequently includes loss of performance, although symptoms vary widely as described above. Similarly, a great variation of signs is found during clinical examination, depending on the degree of underlying heart disease. Cardiac auscultation reveals a totally abnormal rhythm with absence of the fourth heart sound (S4). Intensity of heart sounds can vary from beat to beat. Early systolic murmurs may be detected because of the lack of presystolic AV valve closure (Deegen, 1986; Bertone and Wingfield, 1987). Resting pulse rate is usually normal unless other primary heart disease is present. A pulse deficit is occasionally present. The jugular veins should be examined for signs of elevated right atrial pressure. A small portion of horses present with exercise-induced epistaxis, which may occur with minimal exercise (Deem and Fregin, 1982; Reef et al., 1988).

A definitive diagnosis is made by electrocardiography. In normal horses P wave (atrial depolarisation), QRS complex (ventricular depolarisation) and T wave (ventricular repolarisation) are separated by an isoelectric line. In animals with AF, P wave is absent and the continuous electrical activity in the atria produces undulations of the isoelectric line, known as ‘f’ waves (Fig. 3). R-R intervals are irregular but QRS complexes are supraventricular in origin.

On M-mode and pulsed wave Doppler echocardiography, the A wave, which is produced by the normal atrial contraction, is absent (Wingfield et al., 1980; Stadler et al., 1994).
AF in horses is usually treated with quinidine sulphate, a class 1A antiarrhythmic drug. Quinidine blocks fast sodium channels, prolongs action potential duration and refractory period, and depresses conduction velocity. Treatment is reasonably successful if there is no evidence of underlying heart disease and animals can return to previous athletic ability (Irvine, 1975; Reef et al., 1988). Best results are obtained with recent onset AF (Glendinning, 1965). Success rates of up to 87.5% have been reported (Reef et al., 1988) and recurrence rate varies between 20 and 30% (Deegen and Buntenkotter, 1976; Deem and Fregin, 1982; Reef et al., 1988). Because quinidine also produces hypotension (peripheral vasodilatation) and tachycardia (vagolytic effects), it should not be administered to horses with signs of congestive heart failure. Although quinidine is an antiarrhythmic drug, it also has proarrhythmic properties that may cause syncope as a result of torsades de pointes or even sudden death. In one study, 5% of the horses died during quinidine treatment (Morris and Fregin, 1982).

A dose of 20 mg/kg body weight is administered every two hours via a nasogastric tube until sinus rhythm is restored or a maximal daily dose of 80-130 g is achieved or signs of toxicity develop. In animals that fail to respond to treatment, quinidine treatment may be continued.
at 6 hourly intervals or an additional digoxin treatment may be given to slow down ventricular rate during quinidine treatment (Reef et al., 1995). Concurrent digoxin and quinidine treatment should be given cautiously as this enhances digoxin toxicity (Bertone and Wingfield, 1987; Parraga et al., 1995).

Up to 76% of the horses show quinidine side effects, including urticaria, nasal oedema, anorexia, tachycardia, weakness, ataxia, colic, diarrhoea, laminitis or convulsions (Morris and Fregin, 1982; Reef et al., 1988). ECG recordings prior to quinidine administration are vital: 25% increase in the width of the QRS complex indicates toxicity and precludes further treatment.

Intravenous treatment with quinidine gluconate has also been reported but success rate is slightly lower (Gerber et al., 1971; Deegen and Buntenkotter, 1974; Lekeux et al., 1981; McGuirk et al., 1981; Muir et al., 1990).

Following conversion to sinus rhythm, horses usually are not immediately returned to training. However, the recommended rest period is empirical, not based on clinical findings. Therefore, different authors recommend a period of rest after conversion ranging from a few days (Gerber et al., 1971; Amada and Kurita, 1975), 1 to 2 weeks (Bonagura, 1990; Patteson, 1996), up to 3 months (Rose and Davis, 1977b). In horses, not treated for AF because of congestive heart failure, therapy is best aimed at alleviating the clinical signs of heart failure and, obviously, these animals should avoid any effort.
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Horses can suffer from cardiac rhythm disturbances that can affect their performance or can even be life threatening. Clinically, the most important arrhythmia in equines is atrial fibrillation. During the past decades, only little progress has been made concerning arrhythmias in equines. In general, the surface electrocardiogram (ECG) is the only diagnostic aid while treatment options merely consist of a few drugs, such as quinidine and digoxin. Conversely, in human medicine, extensive facilities are available in the cardiology department. In man, electrophysiological studies and different cardiac pacing techniques have become a mainstay in the diagnosis and treatment of many dysrhythmias. Short-term pacing is applied with temporary catheters while long-term pacing can be achieved by permanent implantation of an electrical pulse generator.

Besides diagnosis and treatment, cardiac pacing also provides an excellent means to study pathophysiology of arrhythmias in animal models.

The aims of our study were investigating the applicability of atrial pacing in horses and subsequently using the technique to study the pathophysiology of atrial fibrillation in equines. Particular aims of this study were as follows:

Section 1: atrial pacing
1. Temporary pacing
   a. Development of a technique
   b. Application in the treatment of atrial flutter
2. Permanent pacing
   a. Development of a technique
   b. Application to treat sinus node dysfunction

Section 2: research on atrial fibrillation
1. Development of a model for chronic atrial fibrillation in healthy equines
2. Application of the model to study the pathophysiology of chronic atrial fibrillation
Temporary transvenous atrial pacing in horses: threshold determination

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SUMMARY

The purpose of this study was to perform temporary atrial pacing and to determine the atrial strength-duration (S-D) curve, which displays the minimal pulse intensity necessary to achieve atrial capture. In seven horses atrial pacing was applied using a temporary pacing catheter and a pacemaker as electrical pulse generator. Using the stimulus reduction method, three approaches for atrial threshold determination were used. With the fixed pulse width method, at several pulse widths the corresponding minimal amplitudes to achieve capture were determined, describing a S-D curve. With the fixed amplitude method, the corresponding threshold pulse widths were determined at several fixed amplitudes. The third method proved to be the best one and was a combination of both aforementioned methods to determine 2 points of the S-D curve. From these two points the whole S-D curve was calculated using a mathematical equation. Temporary pacing can be used to terminate atrial flutter, to induce atrial arrhythmias or to obtain more information about the electrophysiologic properties of the heart such as the atrial refractory period, atrial vulnerability and atrioventricular conduction.
INTRODUCTION

The excitable properties of the cardiac cells make artificial stimulation of the heart possible (Irnich 1989). Artificial stimulation can be performed by mechanical or electrical stimulation. Electrical stimuli are delivered by an external or an implantable pulse generator and are conducted to the heart by means of a lead wire with electrodes on its tip. The transvenous insertion of a lead or catheter electrode into the cardiac cavity is the most widely used method for cardiac pacing, although transcutaneous, transoesophageal or epicardial stimulation are also possible.

The electrical stimulus, which is a square current pulse, has to reduce the resting potential of the cardiac cells by a critical amount and within a critical time in order to reach the threshold for the propagated response, known as the action potential (Trautwein 1975). The threshold for cardiac pacing can be defined as the smallest amount of electrical activity that produces consistent myocardial capture outside the refractory period of the heart (Hayes and Osborn 1996). It is determined by its amplitude or strength and by its pulse width (PW) or duration. Within limits, values with a lower amplitude must have a longer duration, while the duration of high amplitude values may be shorter. These threshold values describe a hyperbolic-like strength-duration curve (Geddes and Bourland 1985). Knowledge of this strength-duration relationship is fundamental to safe and effective cardiac pacing (Ayers et al. 1986). A threshold within normal limits is a means of verifying that the electrode is in a secure position and is in contact with viable cardiac tissue (Schuenemeyer 1986).

Temporary cardiac pacing can be used therapeutically, as during third degree atrioventricular block, to prevent problems during anaesthesia of animals with documented conduction system disease.
or as a treatment of atrial flutter (van Loon et al. 1997). It can also be used to induce atrial arrhythmias in order to study their effect on cardiac function, as performed by Kubo et al. (1975), Senta and Kubo (1978) and Moore and Spear (1987). Furthermore temporary pacing can provide useful information about the electrophysiologic properties of the heart, such as atrial refractory period, atrioventricular conduction (Yamaya et al. 1994, 1997a and 1997b) or atrial vulnerability (Senta and Kubo 1978).

The purpose of this study was to assess the feasibility of temporary atrial pacing in horses, to determine the minimal pulse intensity necessary to achieve atrial stimulation and to evaluate different techniques to determine the atrial S-D curve.
MATERIALS AND METHODS

Threshold values for temporary transvenous atrial pacing were determined in seven healthy standardbred horses. Clinical, electrocardiographic and echocardiographic examinations were normal in all horses.

Instrumentation

A catheter electrode or lead, which possessed two electrodes at its tip, was used for bipolar stimulation of the right atrium. The lead was straight in 3 horses and had a J shaped tip in 4 horses. A pacemaker served as an external pulse generator and was connected with the electrodes of the lead. A programmer had telemetric contact with the pulse generator and was at the same time connected with a surface electrocardiogram (ECG). With the programmer, the pulse generator could be programmed to deliver electrical pulses with a specific interval, amplitude and duration. Furthermore, electrical activity of the heart could be 'sensed' through the same electrode in order to obtain an endocardial electrogram. The endocardial electrogram and the surface ECG were simultaneously visible on the programmer screen and could be recorded on paper.

After local anaesthesia (xylocaine 2 %), an introducer sheath was inserted in the lower third of the jugular vein using a modified Seldinger technique. Via the jugular vein, the catheter electrode was inserted into the cardiac chamber. Location of the catheter tip was confirmed by the ECG recordings and by echocardiography. Initially, while the electrode tip was still in the blood vessels, no or minimal electrical activity could be sensed. Once the electrode entered the right atrium, largest deflections on the endocardial electrogram coincided with the P waves on the surface ECG. Further advancement
of the catheter into the right ventricle produced large endocavitary deflections simultaneous with the QRS-complexes.

On echocardiography, catheter movement was visible once the catheter entered the right atrium. Due to lung interference, the dorsal part of the right atrium could only be imaged partially.

**Lead positioning**

First the lead was inserted into the right atrium and advanced until it reached the tricuspid valve or entered the right ventricle. Subsequently, the lead was withdrawn until large intra-atrial deflections with an equal morphology were present, indicating a stable contact between the electrode and the endocardium. The lead was left in place to perform threshold measurements. When no efficacious electrode position was obtained during withdrawal, when diaphragmatic nerve stimulation occurred or when endocardial contact was lost during threshold measurement, the electrode was repositioned and measurements were repeated.

The whole procedure was performed in the unsedated horse.

**Measurements**

In order to obtain an artificial stimulation of the heart, the pacemaker was programmed to deliver bipolar electrical pulses at a faster rate than the intrinsic heart rate, empirically at 60 beats per minute. The most distal electrode (tip) was used as cathode while the proximal electrode (ring) was the anode. If intrinsic atrial activity was sensed by the pulse generator, stimulation was shortly inhibited to avoid induction of atrial fibrillation.

For the threshold measurements the stimulus reduction method was used. This means that stimulation started with strong pulses, with a long duration and/or high amplitude, and that gradually the intensity of the pulses was decreased until capture, i.e. cardiac contraction, was lost. The decrease of pulse intensity was not continuous but stepwise.
The PW varied in steps of 0.03 milliseconds (ms) between 0.03 and 0.15 ms, in steps of 0.05 ms between 0.15 and 1 ms and in steps of 0.1 ms between 1 ms and 1.5 ms. Variations of the amplitude were restricted to 0.5 volt (V), 1 V, 1.5 V, 2 V, 2.5 V, 3 V, 3.5 V, 4 V, 5 V and 7.5 V.

Three different ways for threshold determination were applied. With the constant PW method (method 1), the pulse duration was programmed at a fixed value. Subsequently, pacing started with stimuli with high amplitude. Every 4 stimuli, the pulse generator gradually decreased the amplitude. Capture was present as long as every electrical pulse was followed by a P wave on the surface ECG. When the pulse amplitude became too low and thus too weak, a P wave was not initiated, capture was lost and intrinsic heart rate reappeared. At that time, stimulation was aborted. The weakest pulse still able to achieve capture was taken as the threshold value for stimulation. The minimal amplitude for stimulation was successively determined at fixed PW of 0.8 ms, 0.6 ms, 0.4 ms, 0.3 ms, 0.2 ms, 0.12 ms and 0.06 ms. A plot of these values, with stimulus strength (V) on the ordinate and duration (ms) on the abscissa, describes the strength-duration (S-D) curve.

With the constant amplitude procedure (method 2), the amplitude of the stimuli was kept constant and the PW was gradually decreased until capture was lost. The minimal PW for stimulation was successively determined at fixed amplitudes of 7.5 V, 4 V, 3.5 V, 3 V, 2.5 V, 2 V and 1.5 V to obtain a new S-D curve.

For the third method, only two threshold values were determined. The constant voltage method was used to determine the threshold PW at a high amplitude pulse, while the threshold amplitude for a long PW stimulus was determined with the constant PW method. With these two values the theoretical strength-duration curve was calculated using a hyperbolic equation, described by Lapicque (1907):
where $I$ is the stimulus intensity (voltage or current), $t$ is the PW, $I_r$ is the rheobase and $t_c$ is the chronaxie.

The rheobase was defined as the lowest amplitude with indefinite pulse duration that just stimulates the myocardium (Irnic 1980). The chronaxie was the threshold pulse duration at a stimulus amplitude of twice that of rheobase. Using equation [1] rheobase and chronaxie can be calculated when 2 threshold values on the S-D curve are known. With the rheobase and chronaxie all points of the S-D curve can be computed using the same equation (Fig. 1.1).

After determination of the S-D curve using these three methods, the lead was advanced again until the tricuspid valve or the right ventricle and was withdrawn to perform a new series of measurements at a second location in the atrium. Thus in each horse 6 S-D curves were determined.

**Statistical analysis**

Statistical comparison of methods 1 and 2 was not performed as variation was along the ordinate for method 1 while variation was along the abscissa for method 2. Therefore, accuracy and precision of methods 1 and 2 were compared with method 3. First method 1 and 3 were compared. At the same fixed PW values as used in method 1, the threshold amplitudes were calculated for method 3 using equation [1] resulting in a variation along the ordinate. Subsequently, to compare methods 2 and 3, threshold PW values for method 3 were calculated for each fixed amplitude used in method 2, resulting in a variation along the abscissa.

Statistical analyses were performed after a loge-transformation of the data to obtain a normal distribution, as indicated by the Wilk-Shapiro/Rankit Plot (Statistix 4.15). For each PW or amplitude level
respectively, a paired $t$-test was performed to compare the accuracy of threshold determination of methods 1 or 2 with method 3 (Statistix 4.1). Similarly, precision of threshold determination with methods 1 or 2, i.e. variances at each fixed level, was compared with precision of threshold determination with method 3 using an F-test (Statistix 4.1). Correlation (Pearson's) was used to determine the degree of linear association between method 1 and 2 with method 3. A probability of $< 0.05$ was considered significant.
RESULTS

Successful atrial pacing was obtained in all horses. Adequate electrode positioning and determination of threshold values could be easily performed. The procedure was well tolerated by the unsedated horse and cardiac pacing initiated no adverse reactions of the horse, even when diaphragmatic nerve stimulation occurred.

The J shaped catheter was found to obtain more easily a stable endocardial contact than the straight lead.

Threshold values for atrial stimulation using the constant PW method and the constant voltage method are listed in Table 1.1 and 1.2, respectively. Geometric mean and 95% confidence interval of each method and the corresponding values of the third method are displayed. The correlation coefficient and p-value of method 1 and method 2 with method 3 are recorded. In addition, Table 1.1 contains rheobasic voltage and chronaxie pulse duration of each horse, and the geometric mean values and the 95% confidence interval, obtained from method 3. The mean rheobase and chronaxie are indicated in Figure 1.1, which displays the mean S-D curve of method 3.

Due to limitations of the system, the amplitude and PW varied stepwise and not continuously. This means that values are overestimated. Furthermore in some horses at a fixed PW of 0.06 ms, threshold amplitude could not be obtained because the threshold was higher than the maximal available strength of 7.5 V. Consequently capture did not occur. In these cases data were excluded from statistical analyses. At a fixed PW of 0.8 ms, the amplitude values of horse 3 might have been lower than 0.5 V but the amplitude could not be decreased further. Similarly for the second method, in some horses the PW values at a fixed amplitude of 4 V and 7.5 V might have been shorter than 0.03 ms but this was the shortest available PW. In some
horses minimal PW for stimulation could not be determined at a fixed amplitude of 2 V and/or 1.5 V because these values were below their rheobase. At an amplitude below the rheobase, even an infinitely long PW will not be sufficient to initiate a depolarisation. In these cases, data were excluded from statistical analyses.

Statistical analyses showed that accuracy and precision at each PW level were similar for both methods 1 and 3 and that there was a linear association between the threshold values of both methods at each PW level (Table 1.1).

Statistical comparison of method 2 with method 3 indicated that precision was similar for both methods at each amplitude level. Also, at each amplitude level, a linear association was found between the threshold values of both methods as indicated by the significant correlation coefficients in Table 1.2. On the other hand, accuracy evaluation showed that threshold values were significantly lower when determined with method 2 at the amplitude levels 1.5, 2 and 2.5 V (Table 1.2).

**Figure 1.1.** This S-D curve displays the geometric mean values and 95% confidence interval (error bars) for all horses and all positions using method 3. The geometric mean values for rheobase and chronaxie are shown.
Table 1.1. Measured amplitude values (V), geometric means (GM) and 95% confidence intervals (95% CI) of the constant PW method, and the rheobase (V) and chronaxie (ms) values with their GM and 95% CI of the third method are displayed for each horse in each position. Values of the GM and 95% CI of the third method are shown. At each PW level, similar superscript letters for the GM values of method 1 and method 3 indicate that no significant difference in accuracy exists between both methods. Correlation (Pearson's), and corresponding p-value, between both methods is shown at each PW level. Some data are missing, indicated by M, because capture could not be achieved at the maximal amplitude of 7.5 V.

<table>
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<th>Horse</th>
<th>Position</th>
<th>Constant pulse width method (Method 1)</th>
<th>Method 3</th>
<th>Rheobase</th>
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| Correlation | | | | | |
| 0.76 | 0.77 | 0.81 | 0.86 | 0.94 | 0.79 | 0.77 | - | - |

| p-value | | | | | |
| 0.011 | 0.001 | < 0.001 | < 0.001 | < 0.001 | < 0.001 | 0.001 | - | - |
Table 1.2. Measured PW values (ms), geometric means (GM) and 95% confidence intervals (95% CI) of the constant amplitude method are displayed for each horse in each position. GM values and 95% CI for the third method are shown. At each amplitude level, different superscript letters for the GM values of methods 2 and method 3 indicate a significant difference in accuracy of both methods. Correlation (Pearson's), and corresponding p-value, between both methods is shown at each PW level. In some horses data are missing, as indicated by M, because capture could not be achieved at the maximal pulse width of 1.5 ms.

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DISCUSSION

During the measurements, factors that could influence the threshold values were avoided as much as possible. The horses were made used to stand in the stocks in order to avoid sympathetic influence. In man, increased sympathetic tone and catecholamines are known to decrease threshold values while increased vagal tone increases threshold values (Preston et al. 1967; Kay 1996). Lignocaine without epinephrine was used as local anaesthetic at the level of the jugular vein, because the sympathomimetic agent epinephrine can lower the threshold for stimulation (Preston et al. 1967; Furman et al. 1977b; Wood and Ellenbogen 1996).

In three horses, a straight lead was used while in four horses measurements were performed with a J tipped lead. The straight lead was found to remain more difficult in stable endocardial contact than the J shaped catheter. The J shape was thought to enhance entanglement in the atrial trabeculae while the catheter was withdrawn. The shape and surface area of the electrodes were identical in both leads, because these parameters influence the threshold for temporary pacing (Irnich 1980; Schuenemeyer 1986). Smaller electrodes have a larger electric field and thus a lower threshold than large surface electrodes (Furman et al. 1977b).

Correct intra-atrial location of the electrodes with a stable endocardial contact is characterized by an endocardial electrogram with large monomorphic deflections concomitant with the peripheral P wave (Furman et al. 1977a). Since voltage threshold increases rapidly with increasing distance between the electrode and the excitable myocardium (Furman et al. 1977b), consistent capture with low threshold values was an additional verification for a good contact between electrode and myocardium. Due to areas of fibrotic
myocardium local variations in threshold values may occur (Furman et al. 1977b; Ector et al. 1985).

Ultrasonography was helpful to position the electrode tip in the atrium but the dorsal part of the right atrium could not completely be visualized. Moreover, even when the catheter was visible on ultrasound, endocardial contact of the electrode tip could not always be assured. While in human medicine fluoroscopy is an important tool to localize the electrode tip, no fluoroscopic control was performed during this study. Due to the large equine thorax, the usefulness of this technique would have been limited in adult horses.

During catheter positioning, single atrial or ventricular extrasystoles occurred occasionally but never initiated sustained dysrhythmias.

Bipolar stimulation means that pulses are delivered between two electrodes within the heart and is most commonly applied for temporary pacing (Wood and Ellenbogen 1996). The most distal (tip) electrode is usually the cathode, while the proximal (ring) is the anode (Furman et al. 1977b; Chou T. C. 1986; Schuenemeyer 1986). The voltage threshold for bipolar pacing is slightly higher than for unipolar pacing although the difference is very small (Furman et al. 1977b).

Immediately after a pulse is delivered, the endocardial electrogram presents a large deflection, known as the afterpotential (Kay 1996). During this deflection the intrinsic electrical activity of the heart is often not visible. Consequently, capture is not always visible on the intracardiac electrogram and can better be established on the surface ECG.

Occasionally, diaphragmatic contractions were seen simultaneous with pacing rate. Stimulation of the lateral, dorsal part of the right atrium, at the level of the diaphragmatic nerve, was likely to be the cause. Decreasing the stimulation intensity, i.e. the amplitude and/or pulse duration, inhibited the diaphragmatic flutter. However, when
diaphragmatic stimulation occurred, measurements were not performed and the lead was repositioned to avoid this phenomenon.

With the stimulus reduction method, stimulation intensity starts at a high level and decreases gradually, while the opposite is true with the stimulus advance method. In human medicine, the stimulus reduction method is mostly used because patients often depend on pacemaker stimulation. Threshold values determined by the stimulus advance method are slightly higher than those of the stimulus reduction method (Sylvén et al. 1982; Schuenemeyer 1986).

For the fixed PW method, method 1, in some horses no capture could be obtained at 0.12 and 0.06 ms because the maximal available amplitude of 7.5 V was not sufficient to achieve capture. Therefore the left side of the curve could not always be obtained and the best results for the fixed PW method were obtained at the right side of the curve. For horse 3, voltage threshold at 0.6 and/or 0.8 ms might have been lower than 0.5 V but 0.5 V was the lowest available amplitude.

For the fixed amplitude procedure, method 2, at low amplitudes there was a large variation in the determined PW values and in some horses no values could be obtained. The reason was that for some horses the low voltage was close to their rheobasic voltage that resulted in a very long PW while in other horses the PW was still very short. And in some horses a threshold PW could not be obtained at a low amplitude because that amplitude was already below their rheobasic voltage. Therefore the fixed amplitude method seemed most suitable for measurement of the left side of the curve, and less appropriate to obtain the right side of the curve.

The third method, which calculated the S-D curve with Lapicque’s law, was a combination of the aforementioned methods in order to simplify S-D curve determination. A point at the left side of the curve was determined with the most suitable method being the fixed amplitude method, while a point at the right side of the curve was measured using the most appropriate fixed PW method. From these
two points rheobase and chronaxie can be calculated using equation [1]. The rheobase is the lowest pulse intensity at infinitely long pulse duration still able to elicit a cardiac contraction. For practical purposes rheobase is usually determined as the threshold stimulus voltage at a pulse width of 2.0 ms (Trautwein 1975; Kay 1996). The lowest rheobase will be achieved when the distance between electrode and excitable tissue is minimal (Geddes and Bourland 1985). The chronaxie is tissue dependent (Ayers et al. 1986) and is a measure of the excitability (Trautwein 1975): the smaller the chronaxie, the more excitable the tissue. It describes where the S-D curve rises with decreasing stimulus duration (Irnich 1980; Geddes and Bourland 1985). When the rheobase and chronaxie are known the whole S-D curve can be quickly synthesized using equation [1]. At all points of the curve this method proved to be comparable with the fixed PW method. The mean values of both methods were different at 0.06 ms but this difference was not significant (p=0.189). The reason for this difference was that for some horses at 0.06 ms the maximal available pulse amplitude of 7.5 V was not sufficient to achieve capture as indicated by 'M' in Table 1.1, by which method 1 underestimated the mean amplitude. Because method 3 calculated the threshold amplitude at 0.06 ms, the mean value was higher and more accurate. When method 3 was compared with the constant amplitude procedure, mean values proved to be significantly different at 1.5, 2 and 2.5 V. This could be explained by the fact that in some horses the fixed amplitude was very close to the rheobasic voltage, resulting in an extremely long PW calculated with method 3. Controversially, for method 2 the mean PW at 2.5 V was longer than the mean value at 2 V. The explanation was that the rheobase of horse 1 in position 2 was 2.39 and thus just below the fixed amplitude of 2.5 V. For method 3 this resulted in a calculated PW of 5 ms, which caused a substantial increase of the mean value. This also explains the large variation along the abscissa in method 3.
Limitations of the study

In this study temporary catheters were used for measurements. Such catheters have no fixation mechanism and small movements of the electrode tip during measurements can change threshold values. This can be prevented using an active fixation electrode to determine thresholds. Such an electrode extends a helix into the endomyocardium to maintain a better endocardial contact.

During our study an implantable pacemaker was used as an external electrical pulse generator. However, this device was not able to deliver electrical stimuli of any desired amplitude or PW and variation was stepwise. Accuracy of the S-D curve determination could be increased using a device that generates pulses of any intensity and with a stepless variation.

This paper describes a method to measure atrial threshold values in horses. These threshold values provide a guide for the required intensity of electrical stimuli to achieve successful cardiac pacing in horses. However, because the threshold values depend on the kind of electrode, the lead, intra-atrial location and also on individual variation, threshold measurements must be determined for each procedure to ensure adequate capture during cardiac pacing. Determination of 2 threshold points and subsequent calculation of the S-D curve using Lapicque's law proved to be the easiest and fastest way to obtain the S-D curve.

Manufacturer's address

1 Temporary Pervenous Lead, Cordis, Miami, Florida, USA
2 Thera D, Medtronic, Minneapolis, USA
3 Programmer 9790, Medtronic, Minneapolis, USA
4 Xylocaïne 2 %, Faculty Vet. Medicine, Merelbeke, Belgium
5 Analytical Software, Tallahassee FL, USA
REFERENCES


Intracardiac overdrive pacing as a treatment of atrial flutter in a horse

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SUMMARY

A 5-year-old Warmblood mare with atrial fibrillation was treated with quinidine sulphate. Atrial rhythm changed into atrial flutter and, since toxic effects occurred, the treatment was discontinued. Seven months after the occurrence of atrial flutter, treatment with a rapid atrial pacing technique restored normal sinus rhythm. One year after the pacing therapy the horse was still in sinus rhythm and was brought back into training. At present, 5 years after the pacing procedure, sinus rhythm is still maintained and no complaints are reported.
INTRODUCTION

Atrial fibrillation is a common type of cardiac arrhythmia in horses. Treatment is mostly attempted by oral administration of quinidine sulphate and is reported to be successful in more than 80 % of the cases. In some horses however, quinidine treatment changes atrial fibrillation into atrial flutter without restoration of normal sinus rhythm (Deem and Fregin 1982). In human medicine, medical therapy of persistent atrial flutter is often disappointing and in those cases a rapid atrial pacing technique can be used to obtain a normal sinus rhythm (Jordaens and others 1993).
CASE HISTORY AND CLINICAL FINDINGS

A 5-year-old Warmblood mare experienced a severe episode of exertional rhabdomyolysis. At the same time a cardiac arrhythmia with severe bradycardia (pulse rate of 16/min) and a cardiac murmur were detected. Since the mare was too weak for transportation, she was kept at rest and was referred to the clinic one month later.

On presentation the horse was in a good condition. The body temperature was normal. Faecal consistency was rather soft. There was no pathologic pulsation of the jugular veins. The pulse rate was 24/min and irregular. A systolic cardiac murmur grade III/VI was audible over the tricuspid valve area. Electrocardiography revealed atrial fibrillation. On echocardiography, subjective assessment indicated a right atrial enlargement. Doppler echocardiography showed a mild tricuspid valve insufficiency. No valvular abnormalities were seen on B-mode or M-mode. Blood analysis was normal. The LDH and LDH1 iso-enzymes were within normal limits.

Since there were no signs of congestive heart failure, a treatment with oral quinidine sulphate was started. After a test dose of 11 mg/kg, the horse was given 22 mg/kg quinidine sulphate every 2 hours for 6 doses. Therapy was continued with 22 mg/kg every 6 hours. On the third day of treatment atrial rhythm had changed into atrial flutter. On the same day intoxication signs occurred and therapy had to be discontinued. During the following days the atrial flutter and the heart murmur remained unchanged. Atrial flutter rate was 185/min, which corresponds to a flutter cycle length (CL) of 324 ms. Ventricular rate was 24/min. Atrioventricular conduction was 4:1 but the conduction was irregular.

The horse returned home and was kept at rest. Seven months after the onset of atrial flutter, the horse was represented and a treatment
with an intracardiac pacing technique was attempted. At that time a systolic cardiac murmur grade III/VI was still present over the tricuspid valve area. A distinct jugular pulsation was visible. Electrocardiography revealed atrial flutter with a flutter CL of 300 ms and a ventricular rate of 24/min with severe second degree AV block. The atrioventricular conduction was approximately 4:1. On echocardiography the right atrial dilatation was more pronounced. Left atrial diameter was normal. On Doppler echocardiography, the tricuspid valve insufficiency was more significant.

**Pacing procedure**

The mare was prepared for cardiac catheterisation. No sedation was used. The left external jugular vein was used to introduce a bipolar pacing catheter (U.S.C.I., Bard, Ireland) into the right ventricle. Into the right external jugular vein a quadripolar pacing catheter (U.S.C.I., Bard, Ireland) was inserted and advanced into the right atrium. Exact positioning of each catheter was obtained both by evaluation of the intracardiac electrocardiogram of each electrode and by echocardiographic control. Subsequently, testing stimuli were applied (Medtronic 5345 DDD Temporary Pulse Generator, Medtronic Inc., U.S.A.) to the atrial and ventricular catheter to check 'capture', i.e. whether stimulation initiated a P-wave and a QRS-complex respectively. A burst of atrial stimuli, 4 - 15 seconds in duration, was given and the effect on ECG was evaluated. The initial stimulation CL was 350 ms which was slightly greater than the flutter CL of 300 ms. Subsequently, as no effect occurred, the CL of pacing bursts was gradually shortened by 30 ms. At a stimulation rate of 230 times per minute, i.e. a pacing CL of 260 ms, atrial flutter changed into atrial fibrillation (Fig. 2.1) and the pacing technique was discontinued.

During the next five days, electrocardiographic examination was performed twice daily. Since there was no spontaneous restoration of sinus rhythm, a treatment with quinidine sulphate was attempted. After three oral doses of 22 mg quinidine sulphate per kg every two hours,
stable atrial flutter waves reoccurred and persisted during the next days.

Before the application of a second overdrive pacing, the horse was twice orally treated with quinidine sulphate (22 mg/kg). After this treatment plasma quinidine level was 4.2 µg/ml. Due to quinidine the flutter CL was now 460 ms. First pacing attempts at a stimulation CL of 360 ms were unsuccessful. Immediately after a pacing burst with a CL of 330 ms, a change in flutter rate occurred. At that time lead II and lead III of the surface ECG resembled very closely atrial fibrillation, while the intracardiac ECG showed a clear flutter wave with a CL of 365 ms (Fig. 2.2).

**Figure 2.1.** During atrial fibrillation intra-atrial waves are completely chaotic and the surface ECG presents typical f-waves (f). (trace 1: atrial electrogram; trace 2: lead II of the surface ECG)

**Figure 2.2.** Clear atrial flutter waves on intra-atrial ECG (arrows) corresponding to P-waves on the surface ECG (P). After a burst of stimuli (small arrows) with capture (P') a change in the atrial rhythm occurs: the surface ECG resembles atrial fibrillation with f-waves (f), while the intracardiac ECG shows atrial flutter with regular flutter waves (arrow-heads). (trace 1: atrial electrogram; trace 2: lead II of the surface ECG)
After an overdrive pacing with a CL of 300 ms, flutter waves continued for a short period and changed suddenly into a normal sinus rhythm (Fig. 2.3). On the ECG a second degree atrioventricular (AV) block was present. The whole pacing procedure was well tolerated by the unsedated horse and one week later it was discharged and kept at rest. An electrocardiographic and echocardiographic control was performed every three months.

Figure 2.3. After overdrive pacing flutter waves continued for a short period (arrows) and changed suddenly into a normal sinus rhythm (arrow-heads). (trace 1: atrial electrogram; trace 2: lead II of the surface ECG)

One year later the mare was re-evaluated. For the previous three months she had been trained everyday for one hour without any complaints. Electrocardiographic examination revealed a sinus rhythm with a second degree AV block. The jugular pulsation had disappeared completely. The systolic murmur over the tricuspid valve area had evolved to grade I/VI. The right atrium was still dilated but its diameter was reduced. On Doppler echocardiography the tricuspid valve insufficiency was less pronounced. At present, 5 years after the pacing procedure, sinus rhythm is still maintained and the owner reports no complaints.
Horses suffering from atrial fibrillation but without other significant cardiac disease usually respond well to quinidine sulphate treatment. A success rate of more than 80% is reported (Deem and Fregin 1982, Reef and others 1988). In these horses, conversion to sinus rhythm sometimes occurs after a short period of atrial flutter (Betsch 1991). However, in some horses (Matsuda 1992), as in the present case, conversion to sinus rhythm does not occur and atrial flutter persists. Atrial flutter is a cardiac arrhythmia that tends to be relatively resistant to medical therapy (Peters and others 1994). Furthermore, because of the vagolytic action and the ability to slow the flutter rate, quinidine therapy can facilitate AV conduction sufficiently to result in a 1:1 ventricular response to the atrial flutter causing ventricular tachycardia or ventricular fibrillation (Fregin 1982, Zipes 1992). This could be an explanation for those horses dying during quinidine therapy as has been reported in literature (Deem and Fregin 1982, Betsch 1991).

Being a reentrant arrhythmia, atrial flutter can be successfully entrained and interrupted by overdrive pacing (Kantharia and Mookherjee 1995, Osborn 1996). In human medicine, rapid atrial pacing is generally considered to be a simple and safe method (Amsel and Walter 1992). Through a venous access a bipolar electrode has to be positioned into the right atrium. In humans accurate positioning is usually performed during fluoroscopy. Since this is barely possible in mature horses, successful positioning was obtained by monitoring the intracardiac ECG to search for the largest endocavitary P-wave deflection and by simultaneous B-mode echocardiography. Since rapid stimulation of the ventricle through an incorrect positioned atrial catheter could cause ventricular fibrillation, exact catheter localisation is essential.
Optimal pacing rate in humans is reported to be 35 - 50 % higher than the mean atrial flutter rate, i.e. at a stimulation CL of 66 - 75 % of the flutter CL (Hii and others 1992, Kantharia and Mookherjee 1995). In this horse restoration of sinus rhythm was obtained at a stimulation CL of 65 % of the mean flutter CL.

In humans, rapid atrial stimulation can change atrial flutter into atrial fibrillation especially at higher stimulation rates (Hii and others 1992, Zipes 1992, Osborn 1996). If atrial fibrillation occurs, overdrive pacing must be discontinued since it is useless in cases of atrial fibrillation. Atrial fibrillation however, is generally better tolerated than atrial flutter (Tucker and Wilson 1993). In humans, 10 - 80 % of the pacing-induced cases of atrial fibrillation convert spontaneously to sinus rhythm. Patients remaining in atrial fibrillation, as this horse, are believed to have a more diseased or abnormal myocardium or cardiac conduction system (Kantharia and Mookherjee 1995).

During a period the surface ECG resembled atrial fibrillation, while the intracardiac ECG revealed atrial flutter. This finding might indicate that some of the horses, which are thought to suffer from atrial fibrillation, have in fact atrial flutter.

It is well known that a long period of atrial flutter or atrial fibrillation in combination with atrial dilatation worsens the prognosis for treatment (Reef and others 1988, Collatos C. 1995, Kantharia and Mookherjee 1995, Stadler and others 1994). Exact measurement of the right atrial diameter is difficult because of a lack of good echocardiographic landmarks. In the present case however, subjective assessment of the right atrial diameter was made by means of videotape analysis of ultrasound images taken by the same investigator. Although these assessments might not represent the exact diameter, they were thought to be an acceptable criterion to evaluate the evolution of the right atrial dimension.
Since antiarrhythmic drugs are believed to improve the results of pacing, quinidine was given prior to the second and successful application of atrial overdrive pacing.

Because temporary asystole can occur immediately after a burst of atrial stimuli, a back-up pacing catheter was inserted into the right ventricle of the horse for safety reasons. If asystole would have appeared, this catheter could deliver stimuli to the ventricle in order to restore a normal ventricular rate.

This is the first report of successful intracardiac overdrive pacing therapy in the horse. It illustrates that a medically resistant and chronically persistent atrial flutter, even in the presence of a marked atrial dilatation, may be converted to sinus rhythm by means of intracardiac overdrive pacing. The pacing technique is well tolerated and could be used to investigate the electrophysiological properties of the heart.
REFERENCES


Dual chamber pacemaker implantation via the cephalic vein in healthy equids

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SUMMARY

The purpose of the present study was to develop a feasible and safe technique for dual chamber pacemaker implantation in healthy horses. Implantation was performed in a standing, tranquilized horse and ponies. Atrial and ventricular leads were transvenously inserted through the cephalic vein and a subcutaneous pacemaker pocket was created between the lateral pectoral groove and the manubrium sterni in 6 equids. Positioning of each lead was guided by echocardiography and by measuring the electrical characteristics of the lead. The implantation procedure lasted about 4 hours in each animal and was well tolerated. In all animals dual chamber pacemaker function was obtained and these results remained good throughout the follow-up period. At the time of implantation atrial and ventricular sensing were between 2.1 and 7.2 mV and 7.8 and 16.8 mV, respectively, and atrial and ventricular pacing thresholds at 0.5 ms varied from 0.5 to 0.7 V and 0.3 to 1.0 V, respectively. Six months after the implantation sensing values varied from 2 to 10 mV for the atrial lead and from 2 to 16 mV for the ventricular lead, while pacing thresholds at 0.5 ms varied from less than 0.5 to 2.5 V for the right atrium and from less than 0.5 to 5.0 V for the right ventricle. Atrial lead dislodgement occurred in 2 animals, requiring insertion of a new lead. Ventricular lead dislodgement was not observed.
INTRODUCTION

A cardiac pacemaker is an implantable device that delivers battery-supplied electrical stimuli through electrodes in contact with the myocardium in order to produce an artificially triggered depolarisation of the atria and/or ventricles.\textsuperscript{1,2} The electrodes can be attached to the epicardial surface, which necessitates a thoracotomy, or can be attached to the endocardium, by means of transvenous lead insertion.\textsuperscript{3} The pacing system contains 1 or 2 leads to perform single chamber or dual chamber pacing. Compared with a single chamber pacemaker, dual chamber systems ensure a more physiological cardiac function.\textsuperscript{2,4} This system not only allows a physiological rate-responsiveness, but also re-establishes atrioventricular (AV) synchrony which preserves the contribution of the atrial contraction to the ventricular filling, preventing systemic and pulmonary venous congestion, decreasing mitral valve regurgitation and thus increasing cardiac output.\textsuperscript{5}

Transvenous lead placement makes cardiac pacing relatively simple and safe and is widely used in human medicine. In small animal medicine, permanent pacing has gained considerable importance in the management of bradycardias caused by third degree atrioventricular (AV) block, high grade second degree AV block (Mobitz type II), sick sinus syndrome or persistent atrial standstill.\textsuperscript{2,4,6-10} Besides the therapeutic use in cases of rhythm disturbances, pacemakers can also be used for diagnostic or investigational purposes. With a pacemaker, electrophysiological measurements can be made and arrhythmias can be artificially induced. Many animal-based studies, using sheep\textsuperscript{11,12}, goats\textsuperscript{13-16}, pigs\textsuperscript{17,18} and especially dogs\textsuperscript{19-23}, have been described but the authors found no published data on equids.
To our knowledge, dual chamber pacemaker implantation in horses has only been described twice for the treatment of a third degree AV block and the applied techniques were quite diverse. In 1986, Reef et al. implanted a dual chamber pacemaker in the ventral neck region of a horse using transvenous electrodes through the jugular vein.\textsuperscript{25} This horse survived for 3 years.\textsuperscript{26} In 1993, Pibarot et al. described the implantation of an atrioventricular pacemaker in a donkey using epicardial electrodes.\textsuperscript{27} They created a subcutaneous pacemaker pocket on the lateral chest wall.

The purpose of the present study was to develop a reproducible technique for dual chamber pacemaker implantation in healthy equids and to investigate the feasibility and safety of the procedure.
MATERIALS AND METHODS

Animals

This study was approved by the Ethics committee of the Faculty of Veterinary Medicine, Ghent University.

Five ponies and a Thoroughbred horse were selected. Body weight and height at the withers ranged between 250 and 440 kg, and 1.25 m and 1.55 m, respectively (Table 3.1). All animals were healthy as indicated by the clinical and biochemical exam. There were no abnormalities on electrocardiographic (ECG) and echocardiographic examination.

Table 3.1. The height at the withers and the characteristics of the leads (Medtronic, Minneapolis, MN) are displayed for each animal. The last column indicates how long the pacemaker had been implanted at the time of submission of the paper.

<table>
<thead>
<tr>
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<th>height (m)</th>
<th>lead</th>
<th>lead length (cm)</th>
<th>polarity</th>
<th>fixation</th>
<th>steroid-eluting</th>
<th>model number</th>
<th>implantation time (months)</th>
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<td>yes</td>
<td>4068</td>
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</table>
CHAPTER 3: Materials & methods

**Equipment**

Dual chamber (DDD) pacemakers\(^a\) were used for implantation. Table 3.1 displays the different lead types that were used. Unipolar as well as bipolar transvenous leads were implanted. For the right ventricle, leads with an active (screw-in) or passive (tines) fixation were used, whereas for right atrial pacing only active fixation leads were applied. Five out of 10 active fixation leads were of the steroid-eluting type (Table 3.1). The length of the implanted leads varied between 52 cm and 110 cm. In the lead body, a stylet could be inserted to supply stiffness and to provide shapeability. During implantation a base apex ECG was continuously recorded\(^b\). Cardiac ultrasonography\(^c\) was performed from the right cardiac window. In order to measure electrical characteristics, including capture threshold at 0.5 ms, lead impedance and sensing voltage of P waves and R-waves, the lead was connected to a pacing system analyser\(^d\) using sterile connector cables. The cathode was connected with the distal (tip) electrode. The anode was connected to the proximal (ring) electrode for a bipolar lead or with the subcutaneous tissue for a unipolar configuration. After implantation lateral radiographs of the chest were obtained to verify the lead position. After 1, 2 and 3 days, after 1 and 2 weeks, after 1, 2 and 6 months and every 12 months, an electrocardiographic and echocardiographic examination were performed. Lead position was verified by echocardiography and special attention was paid for the presence of any irregularity near the lead tip, on the lead body or on cardiac valves that might indicate inflammatory reaction of a fibrinous layer. Color flow Doppler of the tricuspid valve was performed to detect valvular regurgitation. At the same time pacemaker function was analysed using a telemetric pacemaker programmer\(^e\) connected to a surface ECG. Atrial and ventricular sensing threshold was measured during sinus rhythm. Subsequently, atrial and ventricular pacing and sensing were analysed during atrial, ventricular and dual chamber pacing at a pacing rate of 60 beats per minute. For these measurements the sensed and paced
atrioventricular interval were programmed to 350 ms, the atrial and ventricular blanking were 100 ms and 28 ms, respectively, the post-ventricular atrial refractory period was 150 ms and the ventricular refractory period was 300 ms. During the whole follow-up period horses were kept in stalls and every two weeks they were given free access to an arena. The pacemaker was intermittently active to perform cardiac studies, including echocardiographic examinations and blood pressure measurements. Except from horse 1, which developed chronic laminitis, each horse completed treadmill exercise, including performing at walk, trot, canter and gallop, with heart rates up to 175 beats per minute. Horse 2, 3, 4, 5 and 6 completed 12, 4, 16, 12 and 6 treadmill sessions, respectively. Treadmill exercise and free access to an arena started 2 months after implantation.

**Implantation procedure**

The animals were given 15 µg/kg detomidine\(^{1}\) IV and 3 µg/kg buprenorphine\(^{2}\) IV and remained in standing position during the implantation. The horses were placed in stocks to allow the surgeons to sit in a safer position in front of the horse. If the horse showed any discomfort during the implantation, 7 µg/kg detomidine was administered IV. The ventral neck and pectoral region was clipped. The region at the level of the lateral pectoral groove was surgically prepared and was blocked with 2 per cent lidocaine\(^{3}\). An incision of about 8 cm was made along the lateral pectoral groove and the cephalic vein was exposed by blunt dissection. A suture\(^{4}\) was placed around both ends of the exposed vein but only the distal part of the vessel was ligated, preventing blood from the leg entering the surgical site. Between the 2 sutures, a partial venotomy was made (Fig. 3.1). The vein lumen was opened with a vein lifter and the atrial lead, with a straight stylet inserted, was introduced in cardiac direction. The lead was advanced until it became ultrasonographically visible in the right atrium. Subsequently, the ventricular lead, with a straight stylet inserted, was also advanced in the cephalic vein. The lead became
visible in the right atrium and, under echocardiographic guidance, the lead tip was maneuvered into the right ventricular apex. If the lead was fitted with an active fixation mechanism the helix was extended into the myocardium by rotation of a connector pin at the external part of the lead. The lead was connected to the PSA for measurement of electrical variables. Electrical variables for the right ventricular lead were acceptable when the capture threshold did not exceed 1 Volt (V) at 0.5 ms pulse width, the lead impedance was between 400 and 1000 Ohms and the sensed R wave was at least 4.0 mV. For the active fixation leads 5 minutes were allowed to meet the above-mentioned implantation criteria. If electrical parameters did not match these criteria, the lead was repositioned until an acceptable location was reached. The stylet was removed and the lead was further inserted into the vein for about 4 cm to provide sufficient slack. The ventricular lead was secured to the underlying tissue using an anchoring sleeve to protect the lead insulation.

For atrial lead positioning, the stylet was first removed to be curved manually while the lead was left in the right atrium. Re-insertion of this
curved stylet provided a J shape to the lead and supplied body. After connection of the PSA and under echocardiographic control, the lead was slowly manipulated to obtain contact with the endocardium. Once in the right position the helix of the active fixation mechanism was extended into the endocardium and electrical parameters were checked. A good atrial position was achieved when the capture threshold at 0.5 ms did not exceed 1.5 V, lead resistance was between 400 and 1000 Ohms and P wave sensing was at least 1.5 mV. After withdrawal of the stylet, pacing was performed at 5 V and 0.5 ms to check if no diaphragmatic stimulation occurred. If the electrical characteristics did not match the implantation criteria or if diaphragmatic stimulation occurred, the lead was repositioned. If the lead was properly positioned, it was advanced slightly into the vein and the proximal part was secured to the underlying tissue using the anchoring sleeve. Gentle traction was applied to the ventricular and the atrial lead to verify if lead migration occurred and electrical variables were again examined. Subsequently the proximal part of the cephalic vein was ligated. Between the lateral pectoral groove and the manubrium sterni, a subcutaneous pacemaker pocket was created by blunt dissection (Fig. 3.1). The pacemaker was connected to both leads and inserted in the pocket taking care that no acute angulations of the electrodes occurred. Redundant leads were looped along the sides of the device or underneath it. The pocket was irrigated with antibiotics, and the subcutaneous tissue and skin were closed in a routine manner. Flunixin meglumine (0.3 mg/kg IV q8h) and sodium ceftiofur (2 mg/kg IV q24h) were given during 5 days. Oral trimethoprim sulphadiazin treatment (1 mg/kg trimetoprim and 5 mg/kg sulphadiazin PO q12h) was continued for 10 days. During this recovery period, recumbency of the horse was prevented by attaching the horse to the stable wall.
RESULTS

The whole implantation procedure took about 4 hours and was well tolerated. The cephalic vein could be easily exposed and its diameter was sufficiently large to bare both the atrial and the ventricular lead. Positioning of the atrial or ventricular lead often initiated ectopy. However, these arrhythmias were always short lasting and self-terminating. The pacemaker leads could clearly be visualized on echocardiography and on chest radiographs. On the ultrasonographic image, the lead body appeared as a smooth, linear, hyperechoic structure, while the lead tip was characterized by more irregular hyperechoic reflections (Fig. 3.2). However, even if the lead tip was clearly identifiable on echocardiography, the presence of endocardial

Figure 3.2. Right parasternal long-axis echocardiogram optimized to view the right ventricle (RV). The lead body (▽) is visible as a smooth hyperechoic structure underneath the tricuspid valve. The lead tip (◇) is localized in the right ventricular apex and shows more irregular reflections (RVFW = right ventricular free wall; RA = right atrium; RV = right ventricle; IVS = interventricular septum; displayed depth = 12 cm).
contact could not always be ascertained and had to be confirmed by determination of electrical variables. During ventricular lead positioning echocardiographic control was useful to follow the lead entering into the right ventricular apex and to avoid it migrating towards the pulmonary artery. With a straight stylet inserted, the lead easily entered the right ventricular apex (Fig. 3.2) and an acceptable position was readily accomplished. Atrial lead positioning was more difficult. The atrial lead had to curve in the right atrium towards the atrial wall in order to allow the helix to be extended into the myocardium. On echocardiography the most dorsal parts of the right atrium could not completely be imaged and the visualization of both the atrial and the ventricular lead in the right atrium complicated ultrasonographic guidance. Therefore, echocardiography served mainly to prevent atrial lead fixation too close to the tricuspid valve and lead positioning was performed relying mainly on the measurements of electrical variables. Although satisfactory electrical characteristics were often readily achieved after extension of the helix, withdrawal of the stylet sometimes resulted in an immediate loss of capture or sensing, indicating that active fixation of the lead had not been accomplished. Several attempts were sometimes necessary to achieve active fixation of the atrial lead. Furthermore diaphragmatic stimulation occasionally occurred at 5 V and 0.5 ms, which also necessitated lead repositioning. However, lead implantation criteria could always be met (Table 3.2).

On post-operative radiographs the ventricular lead tip was visible in the right ventricular apex in all animals. The atrial lead tip was identifiable in the right atrium and was located in the cranial region of the right atrium in pony 3 and in the horse, in the mid portion in pony 2 and in the caudal part in pony 1, 4 and 5.
Table 3.2. The electrical characteristics of the atrial and ventricular lead at the time of implantation and 6 months after the implantation, including the stimulation threshold at 0.5 ms pulse duration, shown in volts (V) and milliampere (mA), the lead impedance (Ohm, Ω) and the sensing amplitude (mV), are shown for each horse. (* indicates the values of the re-implanted lead)

<table>
<thead>
<tr>
<th>horse</th>
<th>time</th>
<th>atrial lead</th>
<th>ventricular lead</th>
</tr>
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<td></td>
<td></td>
<td>threshold (0.5 ms) V</td>
<td>impedance (Ω)</td>
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<td>1</td>
<td>implantation</td>
<td>0.6</td>
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</tr>
<tr>
<td></td>
<td>6 months</td>
<td>&lt; 0.5 &lt; 0.8</td>
<td>587</td>
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<tr>
<td>2</td>
<td>implantation</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>1</td>
<td>1.3</td>
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<tr>
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<td>implantation</td>
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<td>1.7</td>
</tr>
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<td>6 months</td>
<td>2</td>
<td>3.4</td>
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<tr>
<td>4</td>
<td>implantation</td>
<td>0.7</td>
<td>1.6</td>
</tr>
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<td></td>
<td>6 months</td>
<td>0.5</td>
<td>0.7</td>
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<tr>
<td>5</td>
<td>implantation</td>
<td>0.5</td>
<td>0.8</td>
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<tr>
<td></td>
<td>6 months</td>
<td>0.5</td>
<td>1.3</td>
</tr>
<tr>
<td>6</td>
<td>implantation</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>2.5</td>
<td>3.9</td>
</tr>
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</table>

In all animals the dual chamber pacemaker was successfully implanted and atrial and ventricular sensing and pacing were all achieved, allowing an effective atrial, ventricular and dual chamber pacing function (Fig. 3.3). In the Thoroughbred horse (animal 6), at a heart rate of 30 to 35 beats per minute, the normal intrinsic AV interval was about 400 ms, which is within normal limits. Due to a maximal programmable AV interval of the pacemaker of 350 ms, however, in the dual chamber pacing mode ventricular pacing occurred at slow heart rates although AV conduction in that horse was normal.
All animals had a normal wound healing with formation of a small seroma during the first days post-implantation. Ligation of the cephalic vein caused no circulatory problems and the position of the pacemaker did not impede equids in lying down or performing treadmill exercise. In none of the horses was treadmill exercise associated with lead dislodgement. Atrial lead dislodgement occurred 2 days after implantation in pony 5 causing a loss of atrial capture and atrial sensing. On echocardiography the lead tip was identified in the right ventricle near the tricuspid valve and radiographs were taken to confirm the lead displacement. The pacemaker pocket was reopened and after retraction of the helix, the lead was removed and replaced by a new one. In the horse the atrial lead dislodgement occurred 1 month.
after implantation. At that time treadmill exercise had not been performed. Atrial capture could no longer be obtained, even at 1.5 ms and 7.5 V. Atrial sensing dropped from 8 mV on the previous day, to 1.4 mV on the day of dislodgement. On cardiac ultrasound the dislodged lead tip was identifiable in the right atrium near the tricuspid valve. The lead, which was of the steroid-eluting type, was withdrawn and a new non-steroid-eluting lead was inserted in the contra-lateral cephalic vein. After positioning and fixation of this new lead, the proximal part was tunneled subcutaneously and connected to the pacemaker, restoring normal pacemaker function. Ventricular lead dislodgement was never observed.

Long-term follow-up revealed no abnormalities on echocardiographic examinations. The appearance and position of each lead remained identical. The lead body surface remained smooth and no irregularities were detected near the lead tip. The tricuspid valve showed no valvular lesions or valvular regurgitation. In all animals atrial and ventricular sensing remained possible and both chambers could be successfully stimulated with acceptable threshold values, indicating a good pacemaker function (Table 3.2). Arrhythmias, other than occasional second-degree atrioventricular block, were not seen. In the horse, diaphragmatic stimulation occasionally occurred during atrial pacing. Pony 1 had to be euthanized 1 year after implantation because of a chronic laminitis. Necropsy revealed that both the atrial and the ventricular lead tip were closely attached to the myocardium and were surrounded by a small amount of fibrous tissue. There were no lesions on the tricuspid valve. A small fibrous layer was present on the proximal intravascular part of the lead. A firm fibrous capsule surrounded the pacemaker box.
DISCUSSION

The described standardized technique for dual chamber pacemaker implantation in horses proved to be efficient and safe. The whole procedure could be performed in the standing horse and was well tolerated. Successful sensing and pacing of the atrium as well as the ventricle were obtained on long-term follow-up.

Transvenous implantation of a permanent pacemaker is the preferred method in both human and small animal medicine.\textsuperscript{2,10} In contrast to epicardial lead placement it is much less invasive, cheaper and more rapidly accomplished. A transvenous approach avoids major surgery and can be performed without general anesthesia,\textsuperscript{4,6} which is an advantage in animals with compromised cardiovascular system in which general anesthesia is associated with considerable risk of adverse events\textsuperscript{29,30} The occurrence of a lethal ventricular fibrillation during general anesthesia has been described in a horse during an attempt to implant a pacemaker.\textsuperscript{31} In equids requiring pacemaker implantation because of a symptomatic bradycardia, administration of detomidine could worsen cardiac function because of its negative chronotropic effect. In these animals, a temporary pacing catheter should therefore be inserted into the right ventricular apex prior to sedation, to allow pacing during the implantation procedure.

The only way to perform transvenous pacemaker implantation in equids is to use a superficial vein that is located close to the heart and that is large enough to accommodate 2 leads. The vein will be ligated. Furthermore the pacemaker pocket has to be located close to the vein and close to the heart to avoid the use of extremely long leads and be implanted at a safe location in order to allow recumbency and exercise. For these reasons, the cephalic vein at the level of the lateral pectoral groove was chosen for lead insertion. The left as well as the
right cephalic vein were used without a noticeable difference in the procedure. Although the jugular vein, which was used by Reef et al.\textsuperscript{25}, is also close to the heart, the authors preferred the smaller cephalic vein to be ligated permanently. Consequently, both jugular veins were preserved and venous access was facilitated during subsequent experimental studies. Furthermore, in large breed dogs with lead insertion in the jugular vein excessive neck motion is suspected to be a contributing factor in the higher incidence of lead dislodgement in these animals. \textsuperscript{7,10} The placement of the lead and pacemaker pocket near the \textit{manubrium sterni} was thought to be more stable than localization in the neck. The lateral thoracic vein is large enough to bare 2 leads, but its subcutaneous part is too remote from the heart. Moreover, creating a pacemaker pocket near this vein could impede the use of a girth or recumbency of the horse.

Although complications of the pacemaker pocket were not encountered, the subcutaneous position of the pocket implies a possible risk for injury by biting, rubbing or trauma.

The requisite length of the ventricular lead was about 50 cm for the ponies and about 55 cm for the Thoroughbred horse. Because of the availability of a 110 cm lead, this lead was implanted in the right ventricle of the Thoroughbred horse and redundant lead was looped along the sides of the pacemaker. The atrial lead had to be at least 45 cm for the ponies and 50 cm for the Thoroughbred horse. Passive as well as active fixation leads were used. Passive fixation leads possess tines or fins to enhance entanglement within the trabeculae of the myocardium and were applicable for implantation in the right ventricle. Active fixation leads penetrate the myocardium by grasping screws and they were used for implantation in the right ventricle and the right atrium. Passive fixation leads were never used in the right atrium because we feared that lead dislodgement would occur more easily.

To avoid lead tip distortion, a straight stylet was fully inserted into the lead during introduction and while advancing the lead, to supply a
degree of stiffness and shapeability to the lead. Echocardiography facilitated atrial and ventricular lead positioning, but measurements of electrical parameters were crucial for final adjustments during lead placement because they allow selection of the optimal electrode stimulation and sensing site. For the electrical measurements the distal (tip) electrode of the lead was always connected with the cathode, because cathodal stimulation is less likely to induce arrhythmias. The same acceptance values for the electrical parameters of the atrial and ventricular lead were taken as in human medicine. Because the short- and long-term success of the pacing system is related to the initial lead position, effort was expended to obtain the best possible initial location in terms of both stability and electrical performance. For the active fixation leads, 5 minutes were sometimes allowed for the lead to meet the implantation criteria, because it is common for capture thresholds to decrease significantly shortly after active fixation.

The ventricular lead was positioned first because it may supply back-up pacing in animals with severe bradycardia and because it is usually considered the most important of the leads. Ventricular lead placement was performed with a straight stylet inserted in the lead body to guide the lead tip straight toward the right ventricular apex. Except from an occasional insertion of the tip between the right ventricular wall and a papillary muscle or a migration towards the pulmonary artery, the lead tip readily moved into the right ventricular apex to remain in a stable position. The active as well as the passive fixation leads remained well in place and lead dislodgement was never encountered.

Atrial lead positioning was much more difficult. First because the atrial lead had to bend with its tip toward the atrial endocardium by using a curved stylet and second because a firm endocardial contact had to be obtained with the active fixation mechanism. Even when acceptable electrical parameters were obtained after extension of the
helix, atrial capture was sometimes lost when the stylet was withdrawn. Possibly the helix only partially entered the myocardium, or the lead tip was located parallel to the endocardium instead of perpendicular, preventing the helix to enter the myocardium sufficiently. Furthermore, the presence of large atrial trabeculae might have interfered with the lead fixation. In contrast with the ventricular lead, the exact anatomical position of the atrial lead in the right atrium could not always be determined. However, any atrial position that allows adequate pacing and sensing thresholds can be used as long as no extracardiac stimulation occurs with pacing.\(^5\)

Occasionally, diaphragmatic stimulation was observed during atrial pacing at 5 V and 0.5 ms. Stimulation of the lateral, dorsal part of the right atrium, at the level of the right diaphragmatic nerve, was likely to be the cause.\(^3^4\) When diaphragmatic stimulation occurred the lead was always repositioned.

Fluoroscopy is used during pacemaker implantation in humans and small animals, and could have been helpful during the implantation in horses. Especially during atrial lead placement, fluoroscopy might have been useful to identify the typical to-and-fro motion of the lead tip with atrial activity. However, ultrasonography proved to be sufficient and is also used in human medicine when fluoroscopy is contraindicated, as in pregnant women.\(^3^5\)-\(^3^7\) Post-operative echocardiographic examinations are useful, not only to check lead position but also to look for strands or vegetative lesions, because the latter can often be found in cases of lead infection.\(^3^8\)-\(^4^0\)

Once satisfactory lead position was obtained, the lead was advanced slightly into the vein to impart a small bend and thereby allow for movements of the neck and foreleg that might otherwise exert traction on the lead.\(^1^,^2^,^1^9\) However, care was taken not to enter the lead too far in the vein. Too large a loop may predispose to ectopy, lead displacement or myocardial perforation at the tip.\(^2^,^3\) When securing the outer part of the lead to the underlying tissue and when
closing the pocket, special care was taken not to damage the lead insulation.

After lead implantation, the tissue around the lead tip becomes inflamed due to the presence of foreign material in the body and due to the pressure of the lead-electrode system in contact with the myocardium.\textsuperscript{2,41} With time the inflammatory reaction subsides leaving a thin capsule of fibrous tissue between the electrode and the active myocardium supplying an extra fixation of the lead tip to the myocardium.\textsuperscript{41} However, the inflammatory reaction can be excessive, causing the capture threshold to rise, sometimes above the output of the pacemaker, causing exit block. In this context the use of a steroid-eluting electrode may offer benefits in terms of subacute and chronic thresholds.\textsuperscript{3} Such an electrode elutes small amounts of dexamethasone from its tip which attenuates the local inflammatory reaction and which reduces the thickness of the fibrous capsule that surrounds the electrode, lowering the chronic threshold for stimulation.\textsuperscript{3,33} This study suggests that lower chronic threshold values are observed with the steroid-eluting leads (Table 3.2).

The main complication of the transvenous implantation technique is a lead displacement during the early postoperative period \textsuperscript{4,6,7,10} as it was seen in pony 5. Therefore exercise should be restricted during the first weeks after implantation because at that time a fibrous connection of the lead tip is not yet achieved.\textsuperscript{4,6} In the horse lead dislodgement occurred 1 month after implantation. Such a late dislodgement was probably related to the animal's movement and was caused by inadequate fixation of the anchoring sleeve to the lead or to the surrounding tissue, insufficient slack, or a poor fixation of the lead tip to the endocardium.\textsuperscript{41} The latter could have been influenced by the use of the steroid-eluting electrode in this horse because the elution of dexamethasone could have reduced the thickness of the fibrous capsule surrounding the lead tip.
The maximal programmable AV interval for the pacemaker was limited to 350 ms. In a dual chamber pacing mode, this means that, if the pacemaker hasn’t sensed a ventricular depolarization within 350 ms following an atrial event, a ventricular stimulus will be delivered. At slow heart rates, horses with a normal AV conduction can present a PR interval of more than 350 ms. This implies that, even in the presence of a normal AV conduction, dual chamber pacing can give rise to unnecessary ventricular pacing due to the restricted programmable AV interval. When the heart rate increases slightly, however, PR interval reduces to below 350 ms and inappropriate ventricular pacing ceases.

We can conclude that the implantation of a dual chamber pacemaker using endocardial leads via the cephalic vein is feasible and safe in healthy equids and can be performed on the standing animal. The advantage of the described method is that the cephalic venous access and the subcutaneous implantation of the pacemaker near the manubrium sterni require only minor surgery and can be performed under local anesthesia, avoiding a general anesthesia. The cephalic venous approach preserves both jugular veins, facilitating experimental studies after pacemaker implantation. The subcutaneous position of the pacemaker permits post-operative reprogramming. No major complications were encountered in this study and the implanted pacemakers did not impede the ability of the horse and ponies to lie down, nor to perform treadmill exercise. Limitations of the technique included the lack of fluoroscopy and the limited echocardiographic visualization of the high right atrium, which hampered atrial lead positioning. Implantations were performed in healthy animals and further studies are required to investigate the applicability of the technique in clinical patients who would need temporary pacing prior to sedation. The use of transvenous endocardial leads can imply an increased risk for lead dislodgement. Therefore regular examination of pacemaker function should be performed in a horse with symptomatic bradycardia, especially if the animal is intended to perform exercise.
Although no problems were encountered with pacemaker pockets in this study, the subcutaneously positioned pocket could be injured by external trauma. Besides the implantation of a pacemaker in animals with extreme bradycardia, this relatively simple technique also provides an excellent tool to collect information about cardiac arrhythmias and electrophysiological characteristics of the equine heart. In combination with various drugs, the influence of these drugs on electrophysiological properties of the heart could be studied. Furthermore, arrhythmias can be artificially induced which makes research about their effect on heart function and about the application of a feasible therapy possible.

Acknowledgements

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Footnotes

a Thera D(R), Medtronic, Minneapolis, MN
b Cardiolife TEC-7511K, Nihon Kohden, Tokyo, Japan
c Vingmed CFM 800 SV, GE Vingmed, Horten, Norway
d PSA Model 5309, Medtronic, Minneapolis, MN
e Programmer 9790®, Medtronic, Minneapolis, MN
f Domosedan®, Pfizer Animal Health, Nossegem, Belgium
g Temgesic®, Schering-Plough, Brussels, Belgium
h Xylocaine 2%®, Astra Pharmaceuticals, Brussels, Belgium
i Vicryl 4/1, Johnson & Johnson, Dilbeek, Belgium
j Mersutures 4/1, Johnson & Johnson, Dilbeek, Belgium
k Kanacillin Trifortis Vet®, Continental Pharma, Brussels, Belgium
l Finadyne®, Shering-Plough, Brussels, Belgium
m Excenel®, Upjohn, Puurs, Belgium
n Tribrissen Oral Paste, Mallinckrodt Veterinary, Brussels, Belgium
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Dual chamber rate-adaptive pacemaker implantation in a horse with suspected sick sinus syndrome

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SUMMARY

A 5-year-old gelding presented with syncope at termination of exercise. A 24-hour ECG recording revealed intermittent pauses in the sinus rhythm of up to 10 seconds indicating sinus node disease. Especially at termination of exercise, pauses in sinus rhythm were repeatedly present. A dual chamber rate-adaptive pacemaker was successfully implanted. Rate-adaptive pacing based on a build-in activity sensor, prevented excessive post-exercise bradycardia and syncope, allowing the horse to return to work.
INTRODUCTION

Cardiac pacing is the treatment of choice for many symptomatic bradycardias due to high-degree atrioventricular (AV) block, sick sinus syndrome (SSS) or persistent atrial standstill (Sisson 1989, Sisson and others 1991, Darke 1992, Roberts and others 1992, Neu and Mulch 1994, Kittleson and Kienle 1998, Flanders and others 1999). The implantation of a pacemaker is a relative safe and simple procedure, commonly used, not only in human clinical practice, but also in small animals (Klement and others 1984, Darke 1992, Flanders and others 1999). One of the most important technologic advances in implantation technique has been the development of endocardial leads that can be introduced into the heart from a peripheral vein. Single chamber and dual chamber pacemaker models are available with a variety of programmable pacing modalities. Current pacemakers can vary their pacing rate in response to changes in activity. These types are called rate-adaptive, rate-modulated or sensor-driven pacemakers and are often used in patients with sick sinus syndrome (Barold and Zipes 1992).

In equines, little information is available concerning therapeutic pacemaker implantation. In 1986, Reef et al. performed a successful transvenous implantation of a single chamber model in a horse suffering from third-degree AV block. Sixteen months after the implantation, this model was upgraded to a dual chamber model and continued to function for another 2 years. In 1993, Pibarot et al. implanted a dual chamber pacemaker, using epicardial leads, in a donkey with complete heart block. To the best of our knowledge, no data are available in literature related to the applicability of rate-responsive pacing in equines for symptomatic sinus node dysfunction. We report our experience with the transvenous implantation of a rate-
adaptive dual chamber pacemaker in a horse with syncope due to sick sinus syndrome.
CASE REPORT

History and clinical findings

A 5-year-old gelding was used for dressage and for recreation. During a ride, shortly after a gallop, the horse suddenly collapsed. After a few seconds, the horse was able to stand up again, but still presented a weak gait. The horse was immediately transferred to the Faculty of Veterinary Medicine, Ghent University. At admission, the horse showed a normal behaviour and no abnormalities were seen at walk. During the clinical examination the pulse rate was 22 beats per min (bpm) and slightly irregular. A grade 2/6 holodiastolic murmur was detected over the aortic valve region. Respiratory rate and lung auscultation were normal. No abnormalities were found on neurological examination. Complete blood count and biochemical profile were normal.

Electrocardiography and cardiac ultrasound

An electrocardiogram showed a heart rate of 24 beats per minute with a sinus arrhythmia and an occasional second degree AV block. An echocardiogram, including M-mode and colour flow Doppler showed mild aortic regurgitation. Left ventricular diameter was normal and fractional shortening was 33%. During lunging, the horses’ heart rate increased but immediately after exercise, heart rate dropped very quickly to below 35 bpm and on several occasions pauses in sinus rhythm up to 7 seconds were detected, without a ventricular escape beat occurring. An incremental exercise test on a treadmill revealed a maximal heart rate of 183 bpm. A 24-hour ECG showed sinus bradycardia and occasional second degree AV block. Several episodes of sinus arrest or sinus exit block up to 10 seconds in duration were observed without any ventricular escape beat (Fig. 4.1).
Diagnosis

On the basis of the history, the clinical findings and the ECG results, the diagnosis of SSS with a mild degree of chronotropic incompetence was made. As no other reasons for syncope were found, collapse of the horse was attributed to the sinus node dysfunction.

Treatment and clinical course

A dual chamber rate-adaptive pacemaker was implanted with a previously described technique (van Loon and others 2001). In brief, the horse was placed in the stocks and heart rate was continuously monitored (Cardiolife TEC-7511K, Nihon Kohden, Tokyo, Japan). Before application of sedatives, a temporary bipolar pacing catheter (Temporary Pervenous Lead, Cordis, Florida, USA) was inserted in the jugular vein and was positioned in the right ventricular apex. During the whole implantation procedure, ventricular inhibited pacing was performed at 30 bpm (Investigational model 7218, Medtronic, Minneapolis, USA). After placement of the temporary ventricular pacing catheter, 15 µg/kg detomidine IV (Domosedan; Pfizer Animal Health) and 3 µg/kg buprenorphine IV (Temgesic; Schering-Plough) were administered IV and local anaesthetic was injected at the level of the lateral pectoral groove. The cephalic vein was exposed from the

Figure 4.1. A 24-hour ECG recording with two simultaneous precordial traces demonstrates sinus bradycardia, sinus arrhythmia and a sinus arrest of 10 seconds without any ventricular escape beat. The duration (ms) of each R-R interval is displayed.
surrounding tissue and through a venotomy 2 endocardial bipolar screw-in leads were inserted. Guided by echocardiography from the right hemithorax (Vingmed CFM 800 SV, GE Vingmed, Horten, Norway) and by the intracardiac electrogram, the ventricular (CapsureFix 4068 - 110cm, steroid eluting, Medtronic, Minneapolis, USA) and the atrial active fixation lead (Stela BS45, bipolar, screw-in, atrial endocardial lead, 52 cm, Ela Medical, France) were properly positioned and the screw was extended into the endomyocardium. For the ventricular lead, the threshold for stimulation was 0.6 V at a pulse width of 0.5 ms with an impedance of 600 Ohm at 5 V. The ventricular intracardiac signal was sensed at 6.2 mV. The atrial lead presented a threshold of 0.4 V at 0.5 ms and an impedance of 620 Ohm at 5 V, with a sensing voltage of 5.5 mV. The proximal part of both leads was ligated to the surrounding tissue and connected with the pacemaker, positioned in a subcutaneous pacemaker pocket between the lateral pectoral groove and the *manubrium sterni*. The temporary pacing catheter was disconnected and removed. With a lower rate of 30 bpm, the pacemaker was programmed in the DDI mode, which indicates dual chamber pacing, dual chamber sensing and inhibition of pacing upon atrial or ventricular sensing.

After the implantation, radiography and fluoroscopy confirmed the lead position. The horse remained at rest and was not allowed to lie down for 2 weeks following the implantation. Flunixin meglumine (0.3 mg/kg IV q8h; Finadyne; Shering-Plough) and sodium ceftiofur (2 mg/kg IV q24h; Excenel; Upjohn) were given during 5 days. On the 5th day the horse presented a temperature of 39.2 °C and sodium ceftiofur was continued for another 5 days. Threshold and sensing values were closely monitored. Between 2 and 3 weeks after the implantation, the horse showed an intermittent fever ranging from 38.1 to 38.6°C. Appetite remained normal and no abnormalities were seen at the surgical site or on cardiac ultrasound. During this period however, atrial threshold increased up to 7.5 V at 0.5 ms. The fever was thought to be caused by an inflammatory reaction at the lead tip and 1 mg/kg
oral prednisolone therapy was started (daily for 5 days and every other day for 2 weeks). Fever disappeared and atrial threshold values normalized.

Two months after the implantation, the rate adaptive function of the pacemaker was activated by programming the DDIR mode (Fig. 4.2). Exercise tests at walk, trot and canter were performed, first on a treadmill, afterwards while the horse was ridden by the owner, to search for programming values emulating as close as possible a normal heart rate response both at rest and during exercise. The lowest heart rate was set at 30 bpm and the paced AV interval was programmed at 300 ms. This implicated that the upper sensor-driven heart rate of the pacemaker was 150 bpm. A high threshold for rate adaptation and a low rate response produced the best results. An acceleration time of 1 minute was chosen, which means that, after sensor activation, a slow increase in rate occurs over 1 minute of time. A deceleration time of 2.5 min was selected, which resulted in a gradual decrease in heart rate over 2.5 min after cessation of sensor

Figure 4.2. Surface ECG (1) and marker channel (2) obtained while the pacemaker is in DDIR mode with a paced AV interval of 350 ms. The first complex is still a native beat and atrial (AS) and ventricular sensing (VS) occur. Because sinus node activity decreases, atrial pacing (AP) occurs in the second beat but, as normal AV conduction appears within 350 ms, no ventricular pacing occurs. Because of the slow native heart rate atrial pacing continues in the third and fourth complex, but as the AV conduction slows, no ventricular depolarisation occurs within the paced AV interval of 350 ms and a ventricular stimulus (VP) is delivered.
Dual chamber rate-adaptive pacemaker implantation in a horse with suspected SSS

Long-term monitoring showed sinus bradycardia during exercise. Rate-adaptive pacing was added to the pre-existing atrial pacemaker, which allowed sinus activation. The latter feature prevented the post-exercise bradyarrhythmia, which was repeatedly shown in this horse, and was thought to be essential in preventing exercise-induced syncope in this animal (Fig. 4.3).

The horse returned home. Performance was reported to be normal and syncope was not observed.

Four months after the initial implantation the horse returned to the clinic because of traumatic injury of the pacemaker pocket. Although a normal dual chamber rate adaptive pacemaker function remained present, the pacemaker had to be removed due to contamination of the pocket. This was performed under general anaesthesia and during temporary right ventricular pacing. During this operation, curettage of the pocket was performed. The atrial and ventricular lead were thoroughly rinsed and were inserted in a new pocket, created in the deeper fascia. After the operation, continuous oral clenbuterol treatment (0.8 µg/kg bid, Ventipulmin, Boeringer Ingelheim) was started. A long-term antibiotic treatment (ceftiofur 2 mg/kg IM q24h)

![Figure 4.3. Two post-exercise recordings, each with a surface ECG and a marker channel. Without the pacemaker the horse shows a sinus arrest or sinus exit block of 7 seconds. With the pacemaker in DDIR mode, rate-adaptive pacing prevents post-exercise bradyarrhythmia. (AS = atrial sensing; VS = ventricular sensing; AP = atrial pacing; asterisks indicate paced P waves).](image)
was given in order to try to resolve pocket and lead infection and to avoid the occurrence of endocarditis. After 4 weeks however, fistulation of the pocket recurred. After sedation and analgesia, during temporary ventricular pacing, the pocket was opened. After unscrewing of the lead helix, both leads could be removed with gentle traction. Clenbuterol treatment was continued until, four weeks later, after wound healing, a reimplantation was performed on the contralateral side. Electrical characteristics for the atrial lead (Stelid BS45D 52 cm, bipolar, ELA Medical, France) were a threshold of 1.0 V at 0.5 ms with an impedance of 438 Ohm at 5 V, and a sensing voltage of 5.2 mV. For the ventricular lead (Sweet Tip Rx, 4245-59 cm, bipolar, CPI, Guidant, St.-Paul, USA), a threshold of 1.6 V at 0.5 ms, a lead impedance of 346 Ohm and a ventricular sensing voltage of 3.2 mV. The pacemaker pocket was created slightly more dorsal, underneath the m. cutaneus colli. The horse presented a normal recovery period and returned to his normal work 2 months post-implantation. At the time of submission of this paper, 4 months after the second implantation, the owner reported no complaints and successful dual chamber rate-adaptive pacemaker function remained present.
DISCUSSION

A syncopal episode is defined as a sudden temporary loss of consciousness associated with a deficit of postural tone with spontaneous recovery. Syncope in horses is uncommon and therefore has been virtually unstudied (Crisman 1998).

Sick sinus syndrome (SSS) is a term given to a number of abnormalities of the sinoatrial (SA) node, including persistent spontaneous sinus bradycardia, sinus arrest or SA exit block, combinations of SA and AV conduction disturbances or alternation of paroxysms of atrial tachyarrhythmias and periods of slow atrial and ventricular rates (bradycardia and tachycardia syndrome) (Kapoor 1992, Zipes 1992). Little is known about sinus node disease in horses and its relation to syncope.

In this horse, periods of sinus arrest or sinus exit block up to 10 seconds in duration were seen at rest. Because long periods of sinus arrest were repeatedly demonstrated in the post-exercise period and because the horse had presented syncope at termination of exercise, this bradyarrhythmia was the most likely explanation for the syncopal episode. In humans, postexertional asystole is known to cause syncope (Hirata and others 1987, Huycke and others 1987, Kapoor 1989, O'Connor and others 1999, Crisafulli and others 2000). SSS in human patients generally requires permanent pacemaker implantation and represents the most common indication for pacemaker implantation (Barold and Zipes 1992, Ellenbogen and Peters 1996). In human patients with SSS, it has been proven that atrial based pacing systems (single chamber or dual chamber) are superior to ventricular based pacing (Barold and Zipes 1992, Benditt and others 1995) and this modality was applied in the horse. However, as atrial lead dislodgement represents a potential hazard of endocardial leads
(Sisson 1989, Sisson and others 1991, Darke 1992, Flanders and others 1999), a dual chamber system was implanted. The ventricular lead in this system was considered as an extra safety factor because it would preserve a normal ventricular rate at any time, even if the atrial lead would be dislodged. The use of a rate-adaptive pacing system further expands the treatment possibilities. The described pacemaker was fitted with a sensor, a piezoelectric ceramic crystal, which detects mechanical vibration of the pacemaker box induced by body movements or muscle contractions. Upon sensor activation, pacing rate is gradually increased to a maximal level. At termination of activity, the pacing rate is slowly decreased. Especially the gradual decrease in heart rate was thought to be of importance in this horse to avoid symptomatic bradycardia at termination of exercise, allowing the horse to be ridden again.

The pacemaker pocket was created at the level of the pectoral muscles. This implies that pacemaker vibrations will easily occur even with slight body movements. Therefore, by programming the threshold for rate adaptation at the highest value, the rate adaptive function was set to react slowly and only after vigorous pacemaker vibration, allowing only large sensor signals to increase heart rate. Furthermore, the rate response, which determines the extent to which an increase in the patient’s activity raises the pacing rate, was set to its lowest value. A long acceleration time of 1 minute was chosen and the deceleration time was set at 2.5 min. These values resulted in the best rate-adaptive pacing results and avoided excessive pacing, especially at low activities.

The subcutaneous position of the pacemaker pocket implies that it is vulnerable to external trauma. However, deeper localisation of the pacemaker implies a greater distance between the pulse generator and the programming instrument and may prevent post-operative programming (Fox and others 1986). During the second implantation, the pacemaker pocket was created slightly more dorsal and
underneath the *m. cutaneus colli*, to obtain a better protection against traumatic injury but still allow telemetric programming.

Due to pocket laceration, the pacing system is contaminated. In an ultimate attempt to preserve the leads in the horse, extensive debridement of the pocket and long-term antibiotic treatment were implemented. Although this approach has been described in humans (Hurst and others 1986) and dogs (Sisson and others 1991), antibiotic treatment alone rarely is sufficient to cure infection, and removal of the generator and the leads is usually indicated (Morgan and others 1979). In such patients, a new system may be placed at the time of removal of the infected hardware or a two-step approach may be taken with temporary pacing bridging the time between explantation and the new implant (Lewis and others 1985). However, as SSS in the horse was not an acute life-threatening situation (Barold and Zipes 1992), temporary pacing was not performed. Instead the horse was treated with the $\beta_2$-adrenoreceptor agonist clenbuterol in an attempt to decrease the probability of symptomatic bradycardia (Young and others 1999) during the period of pocket healing.

Administration of the $\alpha_2$ adrenergic agonist detomidine is associated with the occurrence of bradycardia, sinus block and second degree AV block (Clarke and Taylor 1986, Short and others 1986). As drug-induced chronotropic and dromotropic suppression was expected to be emphasized in this horse, administration of detomidine probably would have resulted in syncope due to marked bradycardia. Temporary pacing of the right ventricle allows avoiding syncope by preserving a minimal ventricular rate and should be initiated prior to administration of sedatives. In animals suffering from 3$\text{rd}$ degree AV block temporary ventricular pacing can also be applied as a lifesaving therapy in expectation of a more definitive treatment, i.e. pacemaker implantation.

The DDIR pacing mode was selected for permanent programming, which means AV sequential, non-P-synchronous, rate-modulated
pacing with dual chamber sensing. As AV conduction was normal in this horse, P synchronous pacing (DDDR) was not required. Also in humans with SSS, DDIR pacing is frequently used (Barold and Zipes 1992). The paced AV interval, i.e. the time allowed to elapse between a paced atrial and ventricular complex (if no spontaneous ventricular depolarisation occurs), was programmed at 300 ms. With this value the maximal achievable fully pacemaker dependant heart rate was 150 bpm. Programming of a shorter AV interval would allow a completely paced heart rate of 180 bpm. However, at slow resting heart rates, the AV interval in this horse varied between 300 and 420 ms, which is a normal value in horses. As AV conduction was normal, in the presence of a short paced AV interval, unnecessary ventricular pacing would occur at rest, resulting in impaired hemodynamics at rest (Reynolds 1996) and a reduced battery life. Although the maximal paced heart rate was 150 bpm, during maximal treadmill exercise the horse showed a natural rate of 183 bpm, indicating that a considerable chronotropic response was still present.

We can conclude that dual-chamber pacemaker implantation is a feasible therapy in horses. Rate-adaptive pacing proved to be applicable in horses and was effective to prevent syncope due to post-exertional bradyarrhythmia in this horse.

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Pacing-induced sustained atrial fibrillation in a pony

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SUMMARY

A transvenous screw-in electrode was implanted in the right atrium of a healthy pony and connected with an implantable pulse generator programmed to deliver bursts of electrical stimuli to the atrium. Initially, cessation of burst pacing resulted in short (less than 1 minute) self-terminating episodes of atrial fibrillation. As burst pacing continued, the episodes of induced atrial fibrillation became longer. After 3 weeks of continuous atrial pacing, atrial fibrillation became sustained (56 hours). This model of pacing-induced atrial fibrillation can be used to study the mechanisms leading to atrial fibrillation, its perpetuation and therapy. Our preliminary observations support the concept that once atrial fibrillation starts it sets up changes in the electrical characteristics of the atrium that favour its own perpetuation.
INTRODUCTION

Atrial fibrillation (AF) is the most important symptomatic arrhythmia in horses. It can occur as a result of myocardial disease or valvular insufficiency, but in horses AF is frequently encountered without structural heart disease (lone AF). AF produces adverse hemodynamic effects since atrial contraction is absent and no longer contributes to optimal ventricular filling. During atrial fibrillation electrical activity is continuous and chaotic. The rapid irregular atrial rate is caused by multiple reentrant circuits that produce fibrillating wavefronts sweeping across the myocardial surface (1). In the healthy atrial myocardium the arrhythmia quickly extinguishes itself unless a critical amount of contiguous myocardial surface is present (1). This may explain why AF is more frequently seen in animals with a large heart (e.g. horses) and occurs less in animals with a small heart (1-3).

To study the pathophysiology of AF and possible therapies, many animal models have been developed. Most of them were performed in dogs and have been developed in short-term settings. In these models AF has been maintained by pharmacological or electrical stimulation of the vagal nerve, or after surgically-induced mitral regurgitation or sterile pericarditis (3-6). Recently, chronic AF models have been developed in dogs (5) and goats (7) by means of rapid atrial pacing or intermittent burst pacing. We investigated whether chronic atrial burst pacing in a pony might also lead to an increased atrial vulnerability, thus yielding a model of sustained AF. In the present study an electrical pulse generator was connected to an electrode positioned in the right atrium to deliver bursts of electrical stimuli to the atrial myocardium. The pulse generator was subcutaneously implanted facilitating prolonged atrial pacing.
MATERIALS AND METHODS

A 6-year-old pony mare, weighing 250 kg and measuring 125 cm at the withers, was used for implantation of an electric pulse generator (Itrel II 7424 multi-programmable neurological pulse generator, Medtronic, Minneapolis). Clinical examination was normal. The electrocardiogram (ECG) revealed a sinus rhythm (SR) and no abnormalities were found on echocardiography.

The day of implantation antibiotic prophylaxis was started (15 mg/kg Trimethoprim-Sulfadiazin IV, Borgal®, Hoechst Roussel Vet, Brussels, Belgium). During the whole implantation procedure the pony remained in standing position and was given 20 mg/kg detomidine IV (Domosedan®, Pfizer Animal Health, Nossegem, Belgium) and 2 µg/kg buprenorphine IV (Temgesic®, Schering-Plough, Brussels, Belgium). A base-apex ECG (Cardiolife TEC-7511K, Nihon Kohden, Tokyo, Japan) was connected and cardiac ultrasonography was performed from the right hemithorax. The region of the left lateral pectoral groove was surgically prepared and injected with local anaesthetic. An incision was made along the tract of the cephalic vein. The vein was exposed by blunt dissection of the connective tissue over a length of approximately 3 cm. The distal part of the vein was ligated (Vicryl 4/1, Johnson & Johnson, Dilbeek, Belgium). After a venotomy, a bipolar, active fixation lead (CapSureFix® 4568, Medtronic, Minneapolis) was introduced in the vein and advanced towards the heart. When entrance of the lead tip in the right atrium was visualised on echocardiography, a curved stylet was inserted in the lead body to provide a J shape and to supply stiffness. The external part of the lead was connected with a pacing system analyser (Pacing System Analyser Model 5309, Medtronic, Minneapolis). With the pacing system analyser electrical pulses of variable intensity could be generated and lead impedance and intrinsic cardiac activity could be measured. Subsequently the lead was slowly manoeuvred until
contact with the atrial endocardium was achieved. An appropriated atrial position was obtained when the atrium could be stimulated with electrical pulses not exceeding 1.5 Volt (V) at 0.5 ms pulse width, the lead impedance was between 400 and 1000 Ohms and the sensed P wave was at least 1.5 mV (8, 9). At a stimulation threshold of 0.5 ms, 2.4 mA and 1 V with a resistance of 420 Ohms, and a P wave sensing of 11 mV, the helix of the active fixation mechanism was extended by rotation of a connector pin at the external part of the lead and the stylet was withdrawn. Subsequently, the proximal part of the cephalic vein was ligated and the external part of the lead was secured to the underlying muscle with nonabsorbable material (Mersutures 4/0, Johnson & Johnson, Dilbeek, Belgium). Between the lateral pectoral groove and the manubrium sterni a subcutaneous pocket was created by blunt dissection. After connection of the lead to the pulse generator, the latter was inserted in the pocket, which was closed in a routine manner. Antibiotic treatment (Tribrissen Oral Paste, Mallinckrodt Veterinary, Brussels, Belgium) was continued for 2 weeks.

Four weeks after implantation the stimulator was activated with a programmer (Model 7432 Console Programmer, Medtronic, Minneapolis) and was programmed to apply intermittent burst pacing. Each burst consisted of a 2-second lasting train of electrical stimuli (20 Hz, 2 Volt in amplitude and 0.5 ms pulse width). Every 4 seconds a burst was delivered to the right atrial myocardium.

Measurements were made on the day pacing was started (day 0), after 1 and 3 days and after 1, 2 and 3 weeks. A surface ECG was recorded with a base apex lead and a unipolar lead at the left side of the thorax, 8 cm above the olecranon. The duration of the induced AF episodes was measured by switching the pulse generator off after a burst was delivered, and by recording the time needed for SR to restore. After restoration of SR, the pulse generator was switched on and off again to measure new AF episodes to obtain a mean value and range for the AF duration. On day 0 the pulse generator was
turned on and off 20 times, while on the following examinations, this was only performed for 3 to 5 times. The number of times an atrial response occurred after cessation of the burst was recorded.

This research was approved by the Ethical Committee of the Faculty of Veterinary Medicine.
RESULTS

After full recovery of the pony, the safety of the stimulation program was tested. Burst pacing did not provoke any adverse reactions of the pony. During electrical pacing small stimulation spikes were present on the surface ECG and atrial capture occurred.

Characteristics of the pacing-induced atrial arrhythmia

During the experiment, the configuration of the atrial responses changed. This was best visualised on the unipolar ECG. On day 0 a rapid repetition of electrically induced atrial depolarisations (P' waves) separated by isoelectric segments was seen during and sometimes after the burst, indicating that rapid atrial responses with organised atrial activation were present, rather than AF (Fig. 5.1). On day 0, only in 12 out of 20 bursts, rapid atrial responses were present after cessation of the burst.

Figure 5.1. Surface ECG (unipolar lead on the upper trace and lead II on the lower trace) on day 0. During the burst, small spikes, resulting from the pacing stimulus artefact, and rapid atrial responses are present. The electrically induced atrial depolarisations, P' waves (arrows), are separated by isoelectric segments. After cessation of the burst atrial responses continue during 3 seconds before restoration of sinus rhythm (SR).
From day 1 onwards, clear identification of separate P' waves was no longer possible and the surface ECG showed fibrillation waves and an irregular ventricular response, suggesting that AF was present during and after the burst (Fig. 5.2). From this day onwards, every burst was followed by an episode of AF.

Figure 5.2. Surface ECG (unipolar lead on the upper trace and lead II on the lower trace) after 1 day of burst pacing. The pulse generator is just turned off. AF is present.

**Duration of the pacing-induced atrial arrhythmia**

The day burst pacing was started (day 0), the induced rapid atrial responses were very short lasting and always self-terminating within a few seconds. Over 20 attempts the mean duration of these responses was 1.5 seconds with a range of 0.5 to 3 seconds. After 1 day of pacing the induced AF episodes were short with a mean of 2 seconds ranging from 0.5 to 10 seconds (over 5 inductions) (Fig. 5.3). During the study we observed a progressive increase in the AF duration. On day 3 the mean duration of the induced AF episodes after 5 bursts was 10 seconds (range 2 to 20 seconds). After 1 and 2 weeks of pacing respectively, the mean AF duration had further increased to 6 minutes (range 4 to 8 minutes over 3 attempts) and 10 minutes (range 4 to 15 minutes over 3 attempts). After 3 weeks of burst pacing there was no restoration of SR after inactivation of the stimulator and
Pacing-induced sustained atrial fibrillation in a pony

sustained AF, i.e. AF lasting for more than 24 hours, was present. The pulse generator was left inactive and daily ECG examinations indicated that fibrillation continued. Finally after 56 hours of AF, SR restored spontaneously.

Figure 5.3. Duration of AF in the ordinate (logarithmic scale) versus the time atrial burst pacing is applied. The longer burst pacing is continued, the longer the induced AF episodes. On day 21 sustained AF is present.
Atrial burst pacing with an implantable pulse generator induced episodes of atrial arrhythmia in a healthy pony. Initially the atrial arrhythmia resembled rapid repetitive responses. However, episodes were very short and not every burst was followed by atrial responses. Chronic burst pacing resulted in a changed morphology of the atrial response on the surface ECG: fibrillation waves instead of rapid atrial responses became obvious. The vulnerability of the atria to fibrillation increased and the duration of the induced AF episodes progressively prolonged. Three weeks of burst pacing resulted in sustained AF (> 24 hours).

As AF consists of multiple reentry wavelets, its persistence depends on the number of wavelets that can coexist in the atria (10). When a small number of wavelets are present, the probability that they die out all together is high, and the arrhythmia is likely to terminate itself. The higher the number of wavelets, the smaller the chance they all extinguish simultaneously and the longer AF will persist. The number of wavelets simultaneously present during AF depends on the amount of atrial tissue mass and the wavelength of the atrial impulse (3,7) being the product of conduction velocity and refractory period. In this context, the small size of the pony's heart and therefore the limited amount of atrial tissue may be the underlying reason that the initially induced AF episodes were short (1). In the clinical setting, AF is also encountered more frequently in large breed horses and rather rarely in ponies. Furthermore, many horses have lone AF, i.e. AF without identifiable heart disease, while species with a relatively small heart like humans, dogs and even ponies often present AF in the setting of an underlying heart disease that caused atrial dilatation (1). A progressive increase in AF duration due to chronic burst pacing has also been observed in dogs and goats. Wijffels et al. (7) reported that
chronic burst pacing and AF itself caused a marked shortening in atrial refractoriness, a process referred to as electrical remodeling. The decreased atrial refractory period shortens the wavelength of the atrial impulse and allows more fibrillation waves to coexist in the atria. AF therefore seems to lead to its own progression. Besides a shortening in refractory period, in dogs burst pacing resulted in a slowing of intra-atrial conduction, and thus a shortened wavelength (11), and in an atrial enlargement (5), both leading to an increased AF stability. These elements might also have contributed to the progressive increase in the AF duration in our pony. The above-mentioned observations support the theory that recent onset AF is more likely to convert to sinus rhythm than long standing AF (12).

On day 0, the rapid repetition of P′ waves, separated by isoelectric segments, might have been due to a local reentry in the atrium. But from day 1 onwards, fibrillation waves were visible on the surface ECG indicating the presence of AF. A change in configuration of the atrial response and an increase in the rate of fibrillation have been encountered in goats (7). It was suggested that during the onset of AF the atrium was activated uniformly by broad activation waves, while after chronic burst pacing activation of the atrium had become more complex, by multiple wavelets.

AF is inducible by delivering a single extra-stimulus with a short coupling interval or a burst of electrical stimuli to the right atrium (2,11, 13-17). Until now the inducibility of atrial fibrillation in horses has only been studied with temporary catheters and external pulse generators able to deliver extra-stimuli or bursts of electrical stimuli to the right atrium over a short period of time (2,18). The major limitation of this approach is the short duration of the induced AF episodes and the inability to study the effects of chronic AF over longer periods of time. By the transvenous implantation of a programmable pulse generator under local anaesthesia this problem can be overcome. During our study, burst pacing was only performed during 3 weeks, but, by leaving
the burst program activated, AF can be maintained as long as necessary. In the near future these devices will not only be able to deliver bursts of electrical stimuli but will also allow programmed electrical stimulation with different driving cycle lengths and various coupling intervals of the extrastimuli. This will allow to study the electrical atrial characteristics in more detail. Furthermore, this approach would lead to the development of reliable methods to induce atrial fibrillation. This in term will allow evaluating the effect of different interventions on the inducibility and therefore the prevention of atrial fibrillation. These interventions can include the administration of drugs but also the use of pacing algorithms to prevent atrial fibrillation.

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An equine model of chronic atrial fibrillation: methodology

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SUMMARY

We describe the development and the different features of an experimental model of chronic atrial fibrillation (AF) in equines. In 4 healthy ponies a dual chamber pacemaker, with an adapted pacemaker program, was implanted transvenously in the standing animal. This adapted pacemaker induced episodes of AF by delivering a 2 second burst of electrical stimuli (42 Hz) as soon as sinus rhythm was detected. Simultaneous with a surface ECG, the intra-atrial electrogram could be recorded to determine the atrial electrogram morphology. Programmed electrical stimulation (PES) was used to determine the atrial effective refractory period (AERP) and the rate adaptation of the AERP, the sinus node recovery time (SNRT) and the corrected SNRT, AF vulnerability, AF cycle length and AF duration.

This experimental AF model can be used to study the pathophysiology of chronic AF in equines.
INTRODUCTION

Atrial fibrillation (AF) is a common arrhythmia in horses (Bertone and Wingfield, 1987; Manohar and Smetzer, 1992; Reef et al., 1995) with a prevalence ranging from 0.6% to 5.3% (Holmes et al., 1969; Deegen, 1971; Else and Holmes, 1971; Deem and Fregin, 1982). AF can occur as ‘lone’ AF, i.e. without underlying heart disease, or it can be the result of cardiac pathology. It has been reported that up to 80% of the horses with AF show histopathological lesions on post mortem examination (Else and Holmes, 1971; Kiryu et al., 1974; Kiryu et al., 1977; Deem and Fregin, 1982; Deegen, 1986; Bertone and Wingfield, 1987). On the other hand, about 20% of the horses with AF exhibit no or only minor histopathological lesions, and many of the described lesions also occur in horses without AF (Else and Holmes, 1971; Kiryu et al., 1974; Kiryu et al., 1977; Deem and Fregin, 1982; Bertone and Wingfield, 1987). Furthermore, Reef et al. (1988) reported that about 57% of the horses with AF had no detectable underlying heart disease.

Knowledge of AF in horses is mainly based on findings in horses with naturally occurring AF (Muir and McGuirk, 1984; Marr et al., 1995). It is however impossible to determine whether an animal developed AF due to, possibly distinct, cardiac pathology or whether it represents a real case of ‘lone’ AF. If for instance atrial dilatation or structural changes are found, these could be the cause as well as the consequence of AF. An experimental equine model of chronic AF is therefore needed to study the pathophysiology of this arrhythmia.

In recent years, numerous animal models have been developed to study the pathophysiology of human AF (Janse et al., 1998). In most animal models, acute AF has been studied by applying electrical stimulation of the atria and by pharmacological or electrical stimulation of the vagal nerve, surgically-induced mitral regurgitation or sterile...
pericarditis. These experiments were mainly performed in dogs (Shimizu et al., 1991; Benditt et al., 1994; Sideris et al., 1995; Sokoloski et al., 1997), sheep (Cooper et al., 1993; Maixent et al., 2000) or pigs (Leistad et al., 1993; Leistad et al., 1996). The major limitation of these models has been their failure to sustain AF over prolonged periods. During recent years, however, long-term AF models have been developed in dogs (Morillo et al., 1995; Elvan et al., 1996; Yue et al., 1997), goats (Wijffels et al., 1995), sheep (Willems et al., 2000) and pigs (Qi et al., 2000).

The aims of the present study were to develop a reproducible model of chronic AF in healthy equines and to describe the different features of this model. The application of this model could provide useful information about the pathophysiology of this arrhythmia in equines.
MATERIALS AND METHODS

Equine model of AF

Animal handling was carried out according to The European Directive for Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes. The research was approved by the Ethics Committee of the Faculty of Veterinary Medicine, Ghent University.

Four healthy ponies, aged between 3 and 6 years and between 1.25 m and 1.37 m in height, were selected. Biochemical analysis, clinical examination, electrocardiography and echocardiography were used to exclude animals with structural heart disease.

In all animals, a dual chamber pacemaker was implanted using a previously described technique (van Loon et al., 2001). In brief, the animals were placed in stocks and detomidine (15 µg/kg IV, Domosedan, Pfizer Animal Health) and buprenophine (3 µg/kg IV, Temgesic, Schering-Plough) were administered. A base-apex electrocardiogram (ECG) was continuously recorded (Cardiolife TEC-7511K, Nihon Kohden). After local anaesthesia (lignocain 2%, Xylocaine 2%, Astra Pharmaceuticals), a skin incision was made at the level of the lateral pectoral groove in order to expose the cephalic vein. Through a venotomy, 2 electrode leads (Medtronic) were introduced and positioned in the right atrium and right ventricular apex. Exact positioning of each lead was guided by ultrasonography (Vingmed CFM 800 SV) from the right cardiac window, and by determining the electrical characteristics of each lead with a pacing system analyser (PSA Model 5309, Medtronic), including the threshold for stimulation, the lead impedance, and the voltage of the intracavitary signals. Care was taken not to stimulate the diaphragm during high output atrial pacing.
After correct positioning, fixation of distal end of the lead to the right atrium (screw) and the right ventricle (screw or tines) was achieved. The proximal ends of the leads were secured to the underlying tissue and were connected to a dual chamber pacemaker (Thera D(R), Medtronic). The pacemaker box was positioned in a subcutaneous pocket between the lateral pectoral groove and the cranial part of the sternum. After implantation lead position was verified using radiography and fluoroscopy. Flunixin meglumine (0.3 mg/kg IV q8h; Finadyne, Shering-Plough) and sodium ceftiofur (2 mg/kg IV q24h; Excenel, Upjohn) were given for 5 days. Oral trimethoprim sulphadiazine treatment (1 mg/kg trimethoprim and 5 mg/kg sulphadiazine PO q12h; Tribriessen Oral Paste, Mallinckrodt Veterinary) was continued for 10 days. A recovery period of at least 1 month was allowed.

After full recovery, the normal pacemaker program was modified into a custom made ‘fibrillation’ program (Medtronic). This fibrillation program continuously analyses the intra-atrial and intraventricular electrogram. Below a ventricular rate of 80 beats per minute (bpm), an algorithm was activated that analysed atrioventricular synchrony. Sinus rhythm (SR) was defined as 1/1 AV synchrony during 3 to 4 consecutive heart cycles. Upon SR detection, a 2 second burst of stimuli (42 Hz) was delivered to the right atrium at twice the threshold for stimulation. If, due to burst pacing, rapid irregular atrial activity lasting for more than 1 second was present, AF was considered to be induced (Wijffels et al., 1995). As a result of repeated pacing, the heart was kept continuously in AF. The actual time of burst delivery was stored in the pacemakers’ memory and could be used to assess the duration of the AF paroxysms.

**Electrophysiological measurements**

In all animals, baseline electrophysiological measurements were performed, using a telemetric programmer (Programmer 9790, Medtronic), which allowed simultaneous recording of a surface ECG
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and an intracardiac electrogram. The resting heart rate was recorded to calculate the sinus cycle length (SCL). To determine the threshold for stimulation, pacing was performed slightly faster than sinus rate, 0.5 ms pulse width and high amplitude. Every 8 stimuli, amplitude was decreased. Capture was present as long as every atrial or ventricular stimulus was followed by a P wave or QRS complex, respectively. The lowest output which still captured the atrium or ventricle was taken as the threshold for stimulation. Pacemaker output was subsequently programmed at twice threshold both for electrophysiological measurements and for atrial burst pacing.

To determine the atrial effective refractory period (AERP), programmed electrical stimulation (PES) was performed at twice the threshold amplitude. During pacing (S1-S1) with an interval of 1000 ms, an extrastimulus (S2) was introduced with a coupling interval below the expected refractory period. If no capture of the extrastimulus occurred, i.e. if the S2 was not followed by a P wave on the surface ECG, the S1-S2 interval was slightly prolonged in steps of 8 ms and the procedure was repeated, until capture of the extrastimulus occurred. The longest S1-S2 interval that was not followed by an atrial depolarisation was taken as the AERP (Fogoros, 1995; Morillo et al., 1995). This measurement of AERP was performed at pacing cycle lengths (CL) of 1000, 800, 600, 500, 400 and 333 ms.

To determine the sinus node recovery time (SNRT), at each pacing CL, the pacemaker output was inhibited for a short period until an intrinsic atrial depolarisation occurred. The time between the last paced beat and the first spontaneous atrial depolarisation was recorded. In each animal, this measurement was repeated 3 times at each pacing rate. The longest recorded time was taken as the SNRT (Zipes, 1992). The corrected SNRT (cSNRT) was calculated by subtracting the SCL from the SNRT. The ratio of SNRT and SCL, another index used in human medicine to assess sinus node function, was determined (SNRT/SCL X 100).
To establish baseline AF characteristics, the fibrillation program was briefly switched on and the duration of 3 pacing-induced but self-perpetuating AF paroxysms was recorded. To determine the atrial fibrillation cycle length (AFCL) during AF, the atrial electrogram of an AF episode was recorded on paper. Over a time-window of 1 to 18 seconds, consecutive atrial depolarisations were counted to calculate the mean AFCL. From the recorded atrial electrogram, the AF morphology was determined using the criteria described by Wells et al. (1978). These authors defined more organized AF, with atrial potentials separated by isoelectric segments as Type I AF. Recordings with a similar electrogram morphology but with a disturbed baseline were designated Type II, while Type III AF comprised those with a chaotic pattern without discrete electrograms, indicating a more complex activation pattern. The term Type IV was reserved for cases in which the level of organisation varied over the short period of recording, alternating between Type III and either Type I or II.

When these baseline electrophysiological measurements had been determined, the fibrillation program was permanently enabled during 5 days to verify if AF could be maintained successfully. During this period the ponies were stabled. Daily, the animals’ behaviour was monitored simultaneous with a telemetric ECG recording. On day 5, a re-study was performed determining AF duration, AFCL and AF morphology.
RESULTS

Pacemaker implantation succeeded in all animals. One animal presented atrial lead dislodgement 2 days after implantation, resulting in a loss of atrial capture and atrial sensing. The pacemaker pocket was reopened in this animal and the atrial lead was replaced by a new one. Successful dual chamber pacing was achieved in all animals with a mean atrial and ventricular threshold for pacing of $1 \pm 0.7$ V and $1.9 \pm 2.1$ V respectively.

Baseline electrophysiologic measurements

The mean resting heart rate during sinus rhythm was $42 \pm 5$ bpm which means a SCL of $1439 \pm 185$ ms.

A representative example of an AERP measurement is given in Figure 6.1. In the upper part atrial pacing is performed at 75 bpm, i.e. at a S1-S1 CL of 800 ms. An extrastimulus (S2) is delivered 281 ms after the last S1. This short coupling interval does not result in atrial capture (no P wave). However, an extrastimulus with an S1-S2 coupling interval of 289 ms did capture the atrium as evidenced by a clear P wave on the surface ECG. Consequently, for this horse the AERP was 281 ms. In all animals, the AERP was determined at different atrial pacing rates in order to obtain a rate adaptation curve for the AERP (Fig. 6.2). We observed a marked shortening of the refractory period at increasing pacing rates. At a driving CL of 1000 ms (60 bpm), AERP was $287 \pm 29$ ms. During pacing with an S1-S1 CL of 333 ms (180 bpm) AERP was $234 \pm 20$ ms.

The mean SNRT was $1946 \pm 175$ ms. The cSNRT was $508 \pm 167$ ms and the mean ratio of SNRT to SCL was $137\% \pm 16\%$. 

Figure 6.1. In panel A and B, a marker channel (upper trace) and a surface ECG (lower trace) are displayed from the same animal. Atrial pacing (S1) is performed at 75 bpm, which means at a cycle length of 800 ms. Each pacing stimulus (S1) is followed by a P wave on the surface ECG, indicating capture occurs. In panel A, an extrastimulus (S2) is delivered 281 ms after the last S1 but no capture occurs. In panel B, the S1-S2 interval of 289 ms initiates a P wave (↓). In this animal the AERP at a pacing CL of 800 ms is 281 ms. After each test, sinus rhythm re-establishes and the spontaneous atrial depolarisation is sensed by the atrial lead (AS).

Figure 6.2. Mean values (± standard error) for the AERP at different driving CL in four healthy ponies are displayed on an AERP rate adaptation curve. AERP shortens at shorter driving CL.
Atrial fibrillation study

Activation of the ‘fibrillation’ program resulted in an immediate detection of SR and automatically a 2 second 42 Hz burst of atrial stimuli was delivered (Fig. 6.3). During the bursts, AF was induced as evidenced by the rapid and irregular rate of the f-waves on the surface ECG and the irregular ventricular rhythm. During application of burst stimuli, due to saturation, the intra-atrial electrogram could not be used to evaluate the atrial rhythm. After cessation of the burst, AF was only short lived and terminated mostly within 3 seconds. On the intra-atrial electrogram, the rapid atrial rate during AF became apparent (Fig. 6.3).

![Figure 6.3](image)

**Figure 6.3.** A simultaneous recording of the atrial electrogram (0.2 mV/mm), marker channel and surface ECG (0.05 mV/mm) is displayed. The marker channel indicates when atrial pacing (AP) or when sensing of spontaneous atrial and ventricular activity occurs (AS, VS). The fibrillation program is activated. Upon sinus rhythm detection, a burst (42 Hz) is delivered to the atrium and capture occurs (↓). The induced AF episode is recognized by the pacemaker and inhibits the delivery of a new burst.
The fibrillation program was enabled and AF duration, AFCL and atrial electrogram morphology were measured first at baseline and again after 5 days of continuous AF maintenance (Fig. 6.4). In the normal atria, the induced AF episodes were always self-terminating and the mean AF duration was 3 seconds ± 1 seconds. After 5 days of repeated induction of AF the mean AF duration had increased to 182 seconds (range 6-600 seconds). The mean AFCL was calculated from the atrial electrogram. In acute AF, AFCL was 247 ms ± 33 ms. Due to 5 days of maintained AF, the AFCL shortened to 212 ms (± 27 ms). At baseline, the induced AF episodes were of Type I (n=3) or Type II (n=1). After 5 days of AF, complexity of AF had increased. Type I AF had changed into Type II (n=1) or Type III (n=1) and Type II was transformed into Type III.

Both burst pacing and electrophysiological measurements did not elicit any behavioural reaction of the animal. When observing the animal at rest in a stable it could not be determined when sinus rhythm or AF was present, or when automatic burst pacing occurred.
Figure 6.4. Due to a 5-day period of AF maintenance AFCL shortens, the atrial electrogram becomes more complex and AF duration increases.
DISCUSSION

Main findings

Implantation of a pacemaker, modified with a fibrillation program, proved to be an effective means of inducing AF in healthy equines. Besides repetitive AF induction, electrophysiological parameters, essential for the development and perpetuation of AF, such as the AERP, SNRT, AF duration, AFCL and atrial electrogram morphology, could be studied. As the ponies were apparently completely oblivious to pacing, all measurements could be performed in the conscious, unsedated animal, avoiding any drug-related interference. This also implied that the fibrillation program could remain active day and night in order to maintain AF continuously. In this study, a 5-day period of repeated AF induction increased the AF duration, shortened the AFCL and increased the complexity of the atrial electrogram morphology.

AF research in horses

With a prevalence ranging from 0.6 to 5.3%, AF represents the most important arrhythmia affecting performance in horses (Holmes et al., 1969; Deegen, 1971; Else and Holmes, 1971; Deem and Fregin, 1982). AF is frequently associated with cardiac disease. However, as a number of horses lack evidence of valvular or structural heart disease and because many of them return to their previous level of exercise after AF conversion, lone AF is thought to be present in these animals. However, only few experimental studies investigating the pathophysiology of AF have been performed in equines. Senta et al. (1975) and Senta and Kubo (1978) have reported that temporary rapid atrial pacing could induce short-term paroxysms of AF, perpetuating for a few seconds up to 90 minutes. In 1975, this technique was used to induce short-term AF episodes in 7 healthy horses to study the
effect of AF on the cardiac output (Kubo et al., 1975). However, because the induced AF episodes were always short and self-terminating, cardiac output measurements had to be completed immediately after burst pacing. Moore and Spear (1987) applied atrial burst pacing at a rate of 1800 bpm to induce short episodes of AF in goats, calves, cows and also mules and mature horses to study AF duration and ventricular response during AF.

Only recently, we described the first model of chronic AF in a healthy pony by implantation of a neurostimulator (van Loon et al., 2000). This electrical pulse generator, connected with a right atrial screw-in electrode, was subcutaneously implanted. Every 4 seconds, this pulse generator delivered a 2 second burst of electrical stimuli (20 Hz) to the right atrium. Initially cessation of burst pacing resulted in short self-terminating paroxysms of AF. Three weeks of burst pacing resulted in a sustained AF episode of 56 hours.

Besides the automatic maintenance of AF for a prolonged period of time, the major advantage of the currently described model with the fibrillation pacemaker is the ability to study different electrophysiological characteristics, critical in the development and perpetuation of AF (Morillo et al., 1995; Wijffels et al., 1995; Elvan et al., 1996).

**Pathophysiology of AF**

From human medicine, we know that AF is triggered by ectopic beats, bradycardia or precursor arrhythmias such as atrial tachycardia or atrial flutter (Allessie et al., 2001). Recently, it has been shown that most of the ectopic foci originate from atrial musculature extending in the pulmonary veins or the superior caval vein (Jais et al., 1997; Haissaguerre et al., 1998; Tsai et al., 2000). Whether such foci exist in horses is yet unknown. The role of autonomic balance on the occurrence of AF still remains unclear. These triggers may initiate reentry wavelets, which, meandering through both atria, may interact
with anatomical and/or functional obstacles leading to fragmentation and consequently a source of new wavelets (Allessie et al., 2001). On the other hand, dying out of existing wavelets can be caused by fusion with another wavelet, by reaching the border of the atrium and because the advancing depolarisation wave meets an area where the myocardium has not recovered its excitability from a foregoing activation (Allessie et al., 1985). During AF, a critical number of wavelets is required for self-perpetuating fibrillation. If the number of wavelets simultaneously present in the atria is too small, AF may be short-lived. The more wavelets present at the same time in the atria, the smaller the statistical chance that they die out simultaneously and the more stable AF becomes (Moe, 1962; Wijffels et al., 1995). The number of wavelets depends mainly on the atrial size and on the wavelength of the excitation waves. The larger the atria, the more wavelets they can contain and the more susceptible they become for AF. Besides, the atria can include a higher number of wavelets when the wavelength of each wavelet is decreased. As wavelength is defined as the product of refractory period and conduction velocity, a decrease in these parameters results in a shorter wavelength and an increased AF stability. AF by itself, once initiated, results in a shortening of the AERP, a process referred to as electrical remodeling, and thereby leads to its own progression (Wijffels et al., 1995).

In our study, AERP was determined by applying extrastimuli to the right atrium. When a premature pulse is delivered with a short coupling interval, the tissue is still in the refractory state and the impulse will fail to propagate. The longest coupling interval without propagation of the impulse reflects the effective refractory period (ERP) of that tissue (Fogoros, 1995; Ross and Mandel, 1995). If the coupling interval was any longer, the tissue would be recovered and depolarisation would occur. In the normal pony atria, we determined the AERP at different driving cycle lengths, which demonstrated an AERP shortening at higher heart rates. In other animal models it has been shown that repetitive induction of AF caused a decrease in AERP and that the
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decrease was more pronounced at slower pacing rates (Morillo et al., 1995; Wijffels et al., 1995; Elvan et al., 1996; Willems et al., 2000). In dogs and goats, pacing-induced decrease in AERP and shortening of the wavelength are known to increase AF inducibility and AF perpetuation. In the present model, the induced AF paroxysms were initially short. Five days of repetitive AF induction and presumptive electrical remodeling resulted in an increased AF duration. Furthermore, our ponies showed a decrease in AFCL and thus a higher rate of fibrillation, which was probably related to a pacing-induced decrease in AERP (Morillo et al., 1995). The higher rate of fibrillation and the more chaotic nature of AF resulted in an increased complexity of the atrial electrogram (Fig. 6.4).

In dogs, it has been shown that changes in sinus node function might develop as a consequence of AF (Elvan et al., 1996). Using overdrive suppression, the sinus node function can be established by determining the sinus node recovery time (SNRT). In human medicine, atrial pacing is performed near the sinus node at a rate slightly faster than the basic sinus rate for at least 30 seconds and than abruptly stopped. Due to overdrive pacing, the sinus node can present a pause. The interval from the last paced atrial complex to the first spontaneous sinus node depolarisation represents the degree of overdrive suppression induced by pacing. In humans, the procedure is performed at a series of pacing rates and the longest interval observed is considered to be the SNRT for that patient (Zipes, 1992; Fogoros, 1995). Because the SNRT largely depends on the basic sinus cycle length (BCL) a correction (c) can be made: cSNRT = SNRT – BCL. To measure sinus node function the tip of the catheter should be located close to the sinus node. In the present study, the atrial lead tip was clearly visible on radiography and fluoroscopy but its position in relation to the sinus node was not exactly known. However, as the lead is chronically implanted and thus remains at the same place, several measurements over time might be compared with each other to detect
changes due to AF. As far as the authors know, normal values for SNRT and cSNRT in equines have not been reported yet.

**Clinical implications**

The present study demonstrated the feasibility of developing a reproducible chronic AF model in equines. As lone AF represents a substantial part of the clinical AF cases (Bertone and Wingfield, 1987; Reef et al., 1988), the transvenous approach for pacemaker implantation in healthy subjects, providing a closed-chest animal model and avoiding surgery-related complications such as pericarditis, closely resembled the natural state of AF in equines. Therefore, the present model may enhance the possibility of expanding our understanding of the pathophysiology of AF in equines. Furthermore, this model may facilitate developing new therapeutic strategies.

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Effect of experimental chronic atrial fibrillation in equines

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SUMMARY

In 4 healthy ponies a dual chamber pacemaker, with an adapted pacemaker program, was implanted transvenously. The implantation procedure was performed in the standing, sedated animal. With this pulse generator atrial fibrillation was maintained during 6 months by applying intermittent burst pacing. Electrophysiologic measurements, determination of intracardiac pressure and echocardiography were performed before, during and after the 6-month fibrillation period. All blood pressures and echocardiographic examinations were performed in sinus rhythm during regular atrial pacing. As a result of maintained AF, atrial refractoriness decreased and the rate of fibrillation increased. Additionally, a slight increase in right atrial pressure and a significant left atrial dilatation became apparent. Non-invasive assessment of atrial shortening fraction indicated a total loss of atrial contractile function as a result of fibrillation, which resulted in a decreased stroke volume. During the fibrillation period, the duration of the induced atrial fibrillation paroxysms increased progressively and became persistent in one animal. Duration of the fibrillation episodes was associated with atrial diameter, atrial refractory period and rate of fibrillation.

After restoration of SR, the electrophysiologic parameters returned to normal within 10 days. Atrial size and atrial contractile function normalized only after 1 to 2 months of SR. All fibrillation-induced alterations were reversible within 2 months after cardioversion.
INTRODUCTION

Atrial fibrillation (AF) is the most frequently encountered arrhythmia affecting performance in the horse. Although AF can originate from underlying cardiac disorders such as valvular dysfunction or congenital disorders, this arrhythmia can also affect young healthy horses without detectable heart disease (Amada et al., 1974; Rose and Davis, 1977; Deem and Fregin, 1982; Reef et al., 1988; Detweiler, 1989; Stewart et al., 1990; Collatos, 1995). Especially animals from the latter group often respond well to antiarrhythmic treatment and frequently return to their previous athletic ability (Irvine, 1975; Amada and Kurita, 1978; Reef et al., 1988). Knowledge about AF in horses mainly has been gathered from animals with naturally occurring AF. In these animals, however, the exact duration of the arrhythmia is generally unknown and it is usually not clear whether these horses present, possibly distinct, underlying cardiac pathology. When abnormalities such as atrial dilatation are found in an animal with spontaneously occurring AF it remains to be discussed whether these are cause or consequence of AF.

More information about the pathogenesis of AF in horses might be obtained under more controlled, experimental situations. In the seventies, Senta et al. were able to induce short bouts of AF in healthy horses by applying rapid atrial pacing (Senta et al., 1975; Senta and Kubo, 1978). This technique was subsequently used to study the influence of acute AF on cardiac output (Kubo et al., 1975). Recently, an identical experimental protocol was used to study the effectiveness of an antiarrhythmic drug on acute AF in healthy horses (Ohmura et al., 2000). However, the major limitation of both studies was the short duration of the induced AF episodes, ranging from a few minutes to about one and a half hour.
We recently described 2 experimental models to maintain long-term AF in healthy equines (van Loon et al., 2000; van Loon et al., 2001). In these models, an implanted electrical pulse generator was able to maintain AF continuously by rapid atrial pacing.

The major objective of the present study was validating the applicability of such a model and studying the consequence of long-term AF on electrophysiologic and echocardiographic parameters and on intra-cardiac blood pressures in healthy ponies.
MATERIALS AND METHODS

Animal handling was carried out according to The European Directive for Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes. The research was approved by the Ethics Committee of the Faculty of Veterinary Medicine, Ghent University.

Animals

Four ponies, two mares and two geldings, between 3 and 6 years old and between 1.25 m and 1.37 m at the withers, were selected for the study. Body weight ranged from 250 to 275 kg. These animals showed no abnormalities on clinical and biochemical examination. Electrocardiography and echocardiography, including M-mode and colour flow Doppler, were normal in all animals.

A dual chamber pacemaker (Thera (D)R, Medtronic) was implanted in each animal as described previously (van Loon et al., 2001). After full recovery (at least 1 month), a fibrillation program was uploaded into the pacemakers’ memory. This adapted pacemaker repeatedly induced episodes of AF by delivering a 2 second burst of electrical stimuli (42 Hz) as soon as sinus rhythm (SR) was detected, whereas no stimulation occurred during the induced AF episodes. Transcutaneous programming allowed enabling or disabling the fibrillation program at any time. With the fibrillation pacemaker, AF was maintained during 180 days in each animal.

Experimental protocol

Measurements were performed before AF induction (control values), during the 6 months of AF (effect of AF) and after this AF period when SR was restored (reversibility). First, control measurements were performed in all animals. At this stage, the
fibrillation program was only briefly enabled to induce AF paroxysms in order to study baseline AF characteristics. After the baseline measurements, the fibrillation program was permanently enabled during 6 months to maintain AF. During this period, the fibrillation program was only temporarily disabled to allow SR to restore. Subsequently, electrophysiologic studies, echocardiography and invasive blood pressure monitoring were performed. When these measurements were completed, the fibrillation program was enabled again. After the 180 days of AF, the fibrillation program was permanently disabled to study the reversibility. During this phase, the program was only briefly enabled to restudy AF features.

**Electrophysiology**

Electrophysiologic measurements were performed using a telemetric programmer (Programmer 9790, Medtronic, Minneapolis), which allowed simultaneous recording of the surface ECG and the intracardiac electrogram. Electrophysiological studies were performed at days -2, -1, 0 (control values), at days 5, 10, 20, 30, 60, 120, 180 (AF values), and at days 190, 210 (recovery values).

At baseline and during the reversibility study, first the measurements during SR were performed and afterwards the fibrillation program was temporarily enabled to study AF features. During the fibrillation period (day 0 – 180), first the AF characteristics were documented. After disabling the fibrillation program and spontaneous cardioversion, measurements during SR were carried out.

**Measurements during SR**

Heart rate at rest was determined from a surface ECG and the sinus cycle length was calculated. The threshold for stimulation was determined at 0.5 ms and pacemaker output was programmed at twice diastolic threshold.
Regular atrial pacing was started at 60 beats per minute (bpm), which corresponds to a pacing cycle length of 1000 ms. After 2 min of pacing, the stimulator output was temporarily inhibited until a spontaneous atrial depolarisation occurred. The time between the last paced beat and the first spontaneous atrial depolarisation was recorded to assess the sinus node recovery time (SNRT). This measurement was performed 3 times. Subsequently, programmed electrical stimulation was applied to determine the atrial effective refractory period (AERP). During regular atrial pacing an extrastimulus with a short coupling interval was delivered early in atrial diastole. If the extrastimulus was not captured, the coupling interval was slightly prolonged and the procedure was repeated, until capture of the extrastimulus occurred. The longest coupling interval not followed by an atrial depolarisation was taken as the AERP (Fogoros, 1995; Morillo et al., 1995) at that specific pacing rate. The number of atrial depolarisations that followed the first captured extrastimulus was recorded to assess atrial vulnerability.

The above-mentioned measurements were all performed at atrial pacing rates of 60, 75, 100, 120, 150 and 180 bpm, corresponding to a pacing CL of 1000, 800, 600, 500, 400 and 333 ms, respectively. The longest time from all the SNRT measurements at the different pacing rates was taken as the SNRT of that day (Zipes, 1992). The corrected SNRT (cSNRT) was calculated by the following formula:

\[ cSNRT = SNRT - \text{sinus cycle length} \]

**Measurements during AF**

During AF, mean ventricular rate at rest was calculated. The atrial electrogram was recorded on paper. The local atrial fibrillation cycle length (AFCL) was calculated by measuring the interval between the steepest negative deflections in an 18-second window, averaged to obtain the mean AFCL (Morillo et al., 1995). Shorter time windows were used in case of shorter AF paroxysms. From the recorded atrial
electrogram, the AF morphology was determined using the criteria described by Wells et al. (1978). These authors defined more organized AF, with atrial potentials separated by isoelectric segments as Type I AF. Recordings with a similar electrogram morphology but with a disturbed baseline were designated Type II, while Type III AF comprised those with a chaotic pattern without discrete electrograms, indicating a more complex activation pattern. The term Type IV was reserved for cases in which the level of organisation varied over the short period of recording, alternating between Type III and either Type I or Type II AF.

Subsequently, the fibrillation program was disabled, and the time until sinus rhythm restored spontaneously was recorded as the AF duration. Sustained AF was defined as AF of more than 24 hours (Wijffels et al., 1995).

**Echocardiography**

Echocardiography was performed on days –2, -1, 0 (control period), at days 10, 30, 60, 120, 180 (during the induced AF period), and at days 190, 210, 240 (recovery period after AF).

It should be emphasized that all echocardiographic examinations were not performed during fibrillation, but were completed immediately after spontaneous restoration of sinus rhythm, while regular atrial pacing at a rate of 60 or 75 bpm was performed. Care was taken that no diaphragmatic stimulation appeared during atrial pacing. When second-degree atrioventricular block occurred, measurements during and following AV block were discarded. Cardiac ultrasound was performed from the left and the right thoracic window (Vingmed CFM 800 SV, General Electric, Horten, Norway). Ten cardiac cycles were measured for each variable to obtain a mean value.
**Left ventricular and aortic measurements**

During atrial pacing at 75 bpm, standard echocardiographic measurements were performed (Patteson et al., 1995). Left ventricular internal diameter (LVID) and interventricular septal thickness (IVS) were determined during systole \( (syst) \) and diastole \( (diast) \) from the right parasternal short axis M-mode view. In addition to M-mode views, B-mode echocardiograms were obtained because the ventricular lead occasionally produced an acoustic shadow on the M-mode images. A small dropout on the B-mode image still allowed calliper positioning by extrapolation of the endocardial border. Left ventricular fractional shortening (FS) was calculated from established methods (Feigenbaum, 1986). Fractional wall thickening (FWT) was calculated for the IVS from the formula:

\[
FWT = \frac{IVS_{syst} - IVS_{diast}}{IVS_{diast}} \times 100
\]

Systolic and diastolic left ventricular internal area (LVA) was measured by planimetry from the right parasternal short axis ventricular B-mode images at chordal level. Left ventricular fractional area change (FAC) was calculated from the formula:

\[
FAC = \frac{LVA_{diast} - LVA_{syst}}{LVA_{diast}} \times 100
\]

Systolic aortic diameter was measured by 2-D echocardiography from the right parasternal long-axis left ventricular outflow-tract view at the level of the sino-tubular junction using both the leading-edge to leading-edge method (Sahn et al., 1978) and the inner-edge technique (Schiller et al., 1989).

**Doppler studies**

For the aortic outflow, pulsed wave Doppler spectra were recorded from the left parasternal long-axis 5-chambered view (Long et al., 1992) with the sample volume placed in the centre of the aorta.
Velocity time integral (VTI) and peak velocity ($V_{\text{max}}$) were measured from the Doppler waveforms. Stroke volume was calculated using the equation:

$$\text{Stroke volume} = \text{VTI} \times \text{aortic cross section area}$$

Aortic cross sectional area was calculated using the equation:

$$\text{Aortic cross sectional area} = 3.14 \times \left( \frac{\text{aortic systolic diameter}}{2} \right)^2$$

The leading-edge to leading-edge aortic systolic diameter was used for cardiac output calculation.

Colour flow Doppler from the tricuspid valve and the mitral valve was performed from a left and right parasternal view, respectively (Blissitt and Bonagura, 1995) to assess valvular regurgitation.

**Left atrial measurements**

Left atrial diameters were measured during regular atrial pacing at a rate of 60 and 75 bpm. Left atrial internal diameters were measured from 2-D long-axis left and right parasternal images, optimised to produce the largest diameter of the left atrium using standardised imaging techniques (Long et al., 1992). On the left parasternal views, lung artefacts sometimes blurred delineation of the left atrial lateral wall. Therefore, attention was paid that the coronary vein remained visible throughout the cardiac cycle. Left atrial diameter was measured along a line, parallel to the closed mitral valves, and callipers were placed between the lateral atrial wall near the dorsal part of the coronary vein and the interatrial septum. During a single cardiac cycle, left atrial diameter was measured at specific points in time. Left atrial diameter was determined just prior to atrial contraction, which was at the onset of the P wave on the surface ECG ($\text{LAD}_p$). Subsequently, diameter was measured during maximal atrial contraction ($\text{LAD}_a$), at the end of ventricular diastole ($\text{LAD}_\text{diast}$) and at the end of ventricular
systole (LAD_syst). Shortening fraction of the left atrium was calculated using the equation:

$$\text{Left atrial shortening fraction} = \frac{\text{LAD}_p - \text{LAD}_a}{\text{LAD}_p} \times 100$$

**Invasive blood pressure recordings**

Right heart catheterisation was performed on day 0 (control), day 30 and 180 (AF period), and day 210 and 240 (reversibility).

Similar to echocardiography, all catheterisations were not completed during AF, but were carried out while regular atrial pacing at an arbitrary rate of 75 bpm was performed. Measurements were not made during or following second-degree atrioventricular block. Ten cardiac cycles were measured for each variable to obtain a mean value.

Cardiac catheterisation was performed in the unsedated animal, using a high-fidelity catheter-tip micromanometer (MTC catheter, PPG Biomedical Systems Divisions, Best, The Netherlands). Catheter calibration against a mercury manometer was performed prior to the study. Via an 8.5-F introducer sheath (Intro-flex, Baxter, Germany), the catheter was inserted in the jugular vein and advanced into the right ventricle. Correct catheter position was confirmed by the characteristic pressure trace (van Loon et al., 1994; Nollet et al., 1999). The pressure module (Servomed 104, Hellige, Freiburg im Breisgam, Germany) automatically calculated the first derivative of the obtained pressure recording. Surface ECG, pressure (mm Hg) and rate of pressure change (dP/dt) were simultaneously recorded on paper. After ventricular measurements had been completed, the catheter was slowly withdrawn into the right atrium to obtain atrial recordings. During the entire procedure, the animals’ head position was kept at the same level.

For each cardiac cycle, different variables were calculated from the pressure recordings. For the right ventricle, pressure during atrial
contraction (RV\textsubscript{a}), pressure at end-diastole (RV\textsubscript{diast}), peak systolic pressure (RV\textsubscript{syst}), and the maximal rate of pressure change (RV\textsubscript{dP/dt}) were calculated. For the right atrium, pressure was determined just prior to atrial contraction, which was at the onset of the P wave on the surface ECG (RA\textsubscript{p}), at maximal atrial contraction (RA\textsubscript{a-wave}), at AV valve closure (RA\textsubscript{c-wave}), and at AV valve opening (RA\textsubscript{v-wave}). The maximal rate of pressure change during the atrial contraction (RA\textsubscript{dP/dt}) was recorded. The pressure difference generated by right atrial contraction was calculated from the following formula:

\[
\text{Pressure difference} = RA_{\text{a-wave}} - RA_{\text{p}}
\]

**Statistical analyses**

Statistical analyses for each parameter were done with repeated measures analysis of variance (Proc Mixed, SAS v8, SAS Institute Inc., SAS Campus Drive, Cary, NC, USA). Time was considered a repeated measure, and horse a random effect. An autoregressive covariance structure of order 1 was included in the analyses to take into account correlations between measurements at different time point intervals. A probability of < 0.05 was considered significant.
RESULTS

AF model

In all animals, SR and AF were recognised by the fibrillation program. Burst pacing induced paroxysms of AF. The fibrillation program successfully maintained AF during 6 months. Burst pacing did not elicit any adverse reaction of the animal.

Electrophysiology (Table 7.1)

In each animal, threshold for stimulation remained stable throughout the study.

Heart rate at rest recorded during SR showed a slight, significant increase at days 5, 10 and 120, while the difference was not significant at any other day. Because of the short duration of the AF paroxysms during the control period and the recovery phase, ventricular rate recorded during AF could not be documented accurately. AF resulted in a slight increase in heart rate, but throughout the whole AF period, no significant change in rate was recorded.

SNRT and cSNRT showed no significant changes as a result of AF maintenance. The number of atrial depolarisations that followed the first captured extrastimulus during AERP determination, did not increase significantly due to repeated AF induction.

At baseline, an adaptation of AERP to pacing rate was observed with shorter AERP values at increasing pacing rate (Fig. 7.1). At a driving CL of 800 ms (75 bpm) AERP was 281 ± 31 ms while at a CL of 333 ms (180 bpm) AERP shortened to 229 ± 20 ms, a difference of 52 ms.
Table 7.1. Mean values for electrophysiologic measurements are given. AERP (ms) was measured at different pacing cycle lengths between 1000 and 333 ms. During every AERP measurement the number of atrial depolarisations following the first captured extrastimulus was recorded (+: 1 atrial depolarisation; ++: 2 to 5 depolarisations; +++: more than 5 depolarisations).

<table>
<thead>
<tr>
<th>Day</th>
<th>Control values</th>
<th>Atrial fibrillation period</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-2</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>Heart SR</td>
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<tr>
<td>SR</td>
<td>42</td>
<td>46</td>
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</tr>
<tr>
<td>AF</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>SNRT (ms)</td>
<td>1983</td>
<td>1848</td>
<td>1761</td>
</tr>
<tr>
<td>cSNRT (ms)</td>
<td>136</td>
<td>140</td>
<td>126</td>
</tr>
<tr>
<td>1000</td>
<td>++</td>
<td>+++</td>
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</tr>
<tr>
<td>333</td>
<td>233</td>
<td>229</td>
<td>235</td>
</tr>
</tbody>
</table>

NA: not available; SR: sinus rhythm; AF: atrial fibrillation; (c)SNRT: (corrected) sinus node recovery time (ms)
* indicates significant difference compared to control values with p<0.05

Figure 7.1. Mean values for the AERP at different pacing CL, describing the rate adaptation of AERP. Measurements of day 0 (control) and day 180 (AF) are displayed.
Repeated AF induction resulted in a significant decrease in AERP (Fig. 7.2), although a large inter-individual variation existed. From day 5 onward, the AERP decrease was significant and a plateau was reached after about 2 months of AF. The AF-induced decrease in AERP was more pronounced at slower pacing rates (~46 ms) than at higher pacing rates (~31 ms) (Fig. 7.1). At baseline, the difference between the AERP determined at CL of 800 and 333 ms was 52 ms, while the difference was 23 ms after 6 months of AF. Subsequently, the AERP rate adaptation curve was attenuated. After termination of AF at day 180, within 10 days, AERP values returned to baseline and the normal rate adaptation of atrial refractoriness recurred.

**AF characteristics**

At baseline, AF paroxysms showed a mean AFCL of 247 ± 36 ms (Fig. 7.3). Atrial depolarisations could be clearly identified. Three animals presented Type I AF and one animal Type II fibrillation (Fig. 7.4). As a result of maintained AF, an obvious decrease in AFCL occurred. Two months of AF resulted in an AFCL of 170 ± 16 ms and after 6 months of AF, AFCL had further shortened to 159 ± 16 ms. AFCL was directly proportional to AERP but there was an obvious inter-individual variation. Pony 4 showed a slight decrease in AFCL although AERP values remained virtually unchanged. Maintained AF resulted in a more complex atrial electrogram. Type I AF changed into Type II (n=1) or Type III (n=2). Type II AF changed into Type III (n=1) (Fig. 7.4). At baseline, AF paroxysms were short (Fig. 7.5) with a mean duration of 2 ± 0.5 seconds. Repeated AF induction resulted in a progressive increase in AF duration. After 4 months, mean AF duration was 57 hours, ranging from 18 minutes (Pony 3) to 9 days (Pony 4). Because of maintained fibrillation during 180 days, AF duration ranged from 60 minutes (Pony 3) to 12 hours (Pony 1) and became persistent in Pony 4, requiring defibrillation.
CHAPTER 7: Results

Figure 7.2. Mean AERP values (± standard error) at a pacing CL of 800 ms (* indicates significant difference compared to control values).

Figure 7.3. Mean AFCL (± standard error) during the study.

Figure 7.4. AF type at baseline and at the end of the AF period.

Figure 7.5. AF duration for each animal is displayed throughout the study. AF was maintained from day 0 to day 180.
Echocardiography

**Left ventricle – Aorta (Table 7.2)**

Following maintained AF, left ventricular internal diameter at end-diastole (LVID$_{\text{diast}}$) decreased and internal diameter at end-systole (LVID$_{\text{syst}}$) increased although both differences were not significant. Left ventricular fractional shortening, however, was significantly decreased from day 10 onward (Fig. 7.6). Similar results were obtained for left ventricular internal area. A non-significant decrease in diastolic area and increase in systolic area, and a significant decrease in left ventricular area change were observed. Interventricular septal thickness during systole decreased significantly, while diastolic septal thickness showed no significant changes. Septal fractional wall thickening was not significantly decreased.

No change was observed in the aortic systolic diameter at sino-tubular junction, determined with the leading-edge to leading-edge method as well as with the inner-edge technique.

**Pulsed wave and colour flow Doppler (Table 7.2)**

As a result of experimentally induced atrial fibrillation, spectral Doppler recordings from the aortic outflow showed a significant decrease in both maximal velocity and velocity time integral from day 10 onward. Because no change in aortic systolic diameter was observed throughout the study, the significant decrease in velocity time integral is accompanied by a significant decrease in stroke volume (Fig. 7.6).

No evidence of significant tricuspid or mitral valve dysfunction was observed at either baseline or restudy on colour flow Doppler.
Table 7.2. Echocardiographic measurements of left ventricular internal diameter (LVID; cm) and area (LVA; cm) with calculated left ventricular fraction shortening, of interventricular septal thickness (IVS; cm) and of aortic diameter (cm) and flow.

<table>
<thead>
<tr>
<th>Day</th>
<th>Control values</th>
<th>Atrial fibrillation period</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-2 -1 0 10 30 60 120 180</td>
<td>190 210 240</td>
<td></td>
</tr>
<tr>
<td>LVID</td>
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<td></td>
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<tr>
<td>B-mode</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>diast</td>
<td>8.4 8.5 8.4</td>
<td>8.2 8.3 8.3 8.3 8.1</td>
<td>8.4 8.3 8.3</td>
</tr>
<tr>
<td>syst</td>
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<td>5.7 5.9 6.1 5.9 5.7</td>
<td>5.9 5.5 5.5</td>
</tr>
<tr>
<td>FS</td>
<td>34.3 34.7 33.7</td>
<td>31.0 29.1 26.9 29.4 29.4</td>
<td>30.9 33.5 33.5</td>
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<tr>
<td>M-mode</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diast</td>
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<td>8.2 8.1 8.2 8.3 8.2</td>
<td>8.3 8.3 8.4</td>
</tr>
<tr>
<td>syst</td>
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<td>5.8 5.9 6.0 5.9 5.8</td>
<td>5.6 5.7 5.5</td>
</tr>
<tr>
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<td>32.0 32.3 33.8</td>
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<tr>
<td>IVS</td>
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<td>B-mode</td>
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<td></td>
</tr>
<tr>
<td>diast</td>
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<td>2.3 2.3 2.2 2.2 2.3</td>
<td>2.3 2.4 2.4</td>
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<td>2.4 2.4 2.4 2.3 2.3</td>
<td>2.4 2.5 2.4</td>
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<td>3.0 3.0 3.0 3.0 3.0</td>
<td>3.2 3.3 3.3</td>
</tr>
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<td>20.6 20.5 19.8 22.1 22.1</td>
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<tr>
<td>LVA</td>
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<tr>
<td>B-mode</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diast</td>
<td>39.2 41.1 39.1</td>
<td>41.0 40.8 40.0 39.6 36.3</td>
<td>38.2 37.4 38.1</td>
</tr>
<tr>
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<td>17.4 19.1 19.6 19.1 17.5</td>
<td>17.0 15.1 15.4</td>
</tr>
<tr>
<td>FAC</td>
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<tr>
<td>B-mode</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>6.0 6.1 6.0</td>
</tr>
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</tr>
<tr>
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</tr>
<tr>
<td>VTI</td>
<td>25.4 25.2 25.0</td>
<td>22.2 22.0 20.3 20.9 20.1</td>
<td>23.6 25.3 25.2</td>
</tr>
</tbody>
</table>

FS: fractional shortening (%); FWT: fractional wall thickening (%); FAC: fractional area change (%); LELE: leading-edge to leading-edge technique (cm); IE: inner edge technique (cm); Vmax: maximal flow velocity (m/s); VTI: velocity time integral (cm)

(bold, underlined values differ significantly from baseline p<0.05)

Figure 7.6. Left ventricular fractional shortening (FS) and stroke volume (SV) are displayed. AF was maintained between day 0 and day180.
**Left atrium (Table 7.3)**

Left atrial diameters were determined during atrial pacing at both 60 and 75 bpm. Due to the shorter diastolic time at a rate of 75 bpm, the rapid ventricular filling phase in early diastole was immediately followed by an atrial contraction. As both events occurred as a single smooth movement and could not clearly be distinguished, left atrial diameter before initiation of atrial contraction (LAD<sub>p</sub>) could not be determined accurately at 75 bpm and was only measured during atrial pacing at 60 bpm. Consequently, left atrial shortening fraction was only calculated for the latter rate.

Left atrial diameters obtained at different time points during the cardiac cycle, measured from the left parasternal as well as from the right parasternal views, at a rate of 60 as well as 75 bpm, showed a significant increase in diameter from day 10 or day 30 onward. Figure 7.7 shows different atrial diameters obtained from a left parasternal view at a pacing rate of 60 bpm. At baseline, left atrial diameter at the onset of atrial contraction (LAD<sub>p</sub>), at the end of ventricular diastole (LAD<sub>diast</sub>) and at the end of ventricular systole (LAD<sub>syst</sub>) was 7.8 ± 0.47, 7.5 ± 0.36 and 8.9 ± 0.51 cm, respectively. After 6 months of maintained AF, diameters had increased to 8.6 ± 0.38, 8.9 ± 0.23, and 9.6 ± 0.50 cm, respectively, which means an increase of 0.8, 1.4 and 0.7 cm. The most obvious increase in diameter occurred for left atrial diameter during atrial contraction (LAD<sub>a</sub>). At baseline this diameter was 6.7 ± 0.35 cm while at the end of the AF period it was 8.7 ± 0.39 cm, an increase of 2.0 cm. During the control period, atrial contraction was able to decrease atrial diameter by 1.1 cm, representing a left atrial shortening fraction of 13.4 ± 3.2 % (Fig. 7.8). Ten days of AF were already sufficient to result in a significantly decreased atrial inotropy. Because of long-term AF, atrial contraction no longer resulted in a decrease in atrial diameter. Atrial shortening fraction became negative (-0.9 ± 1 %) indicating that a slight increase in atrial diameter occurred even though the atrium was contracting maximally.
Table 7.3. At an atrial pacing rate of 75 bpm and 60 bpm, mean left atrial diameters (LAD; cm), measured at the end of ventricular diastole (diast) and systole (syst), immediately before the onset of atrial contraction (p) and at maximal atrial contraction (a), were recorded and atrial shortening fraction (FS; %) was calculated.

<table>
<thead>
<tr>
<th>Day</th>
<th>Control values</th>
<th>Atrial fibrillation period</th>
<th>Recovery</th>
</tr>
</thead>
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<tr>
<td></td>
<td>-2  -1  0</td>
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<td>190  210 240</td>
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<td>LAD Right view</td>
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<td>8.3*  8.3*</td>
</tr>
<tr>
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<td>5.6  5.5  5.7</td>
<td>6.1  6.6*  6.7*</td>
<td>6.6  7.2*</td>
</tr>
<tr>
<td>LAD Left view</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diast</td>
<td>7.6  7.5  7.6</td>
<td>8.0*  8.1*  8.2*</td>
<td>8.3*  8.5*</td>
</tr>
<tr>
<td>a</td>
<td>6.7  6.8  6.7</td>
<td>7.5*  7.8*  7.9*</td>
<td>7.9*  8.3*</td>
</tr>
<tr>
<td>ATRIAL PACING RATE 60 BPM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diast</td>
<td>6.5  6.5  6.5</td>
<td>7.1*  7.2*  7.4*</td>
<td>7.5*  7.6*</td>
</tr>
<tr>
<td>syst</td>
<td>7.8  7.9  7.9</td>
<td>8.2*  8.3*  8.4*</td>
<td>8.3*  8.6*</td>
</tr>
<tr>
<td>p</td>
<td>6.4  6.3  6.4</td>
<td>6.7*  6.8*  6.8*</td>
<td>6.8*  7.1*</td>
</tr>
<tr>
<td>a</td>
<td>5.3  5.3  5.3</td>
<td>6.6*  6.6*  6.8*</td>
<td>6.8*  7.1*</td>
</tr>
<tr>
<td>FS</td>
<td>16.5 16.3 16.5</td>
<td>2.1*  2.1*  1.1*</td>
<td>-0.1* -0.5*</td>
</tr>
<tr>
<td>LAD Left view</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diast</td>
<td>7.4  7.7  7.5</td>
<td>8.5*  8.6*  8.6*</td>
<td>8.6*  8.9*</td>
</tr>
<tr>
<td>syst</td>
<td>8.9  8.9  8.9</td>
<td>9.3*  9.3*  9.3*</td>
<td>9.3  9.5*  9.6*</td>
</tr>
<tr>
<td>p</td>
<td>7.8  7.8  7.8</td>
<td>8.0  8.1  8.2</td>
<td>7.9  8.6*</td>
</tr>
<tr>
<td>a</td>
<td>6.7  6.7  6.7</td>
<td>8.0*  8.1*  8.2*</td>
<td>8.0*  8.7*</td>
</tr>
<tr>
<td>FS</td>
<td>13.5 13.0 13.8</td>
<td>0.4*  0.6*  0.3*</td>
<td>-0.5* -0.9*</td>
</tr>
</tbody>
</table>

(* indicates statistically significant difference compared to control values p< 0.05)

Figure 7.7. Left atrial diameters obtained from a left parasternal view, at a pacing rate of 60. Left atrial diameter during atrial contraction (LAD_a) shows the largest increase in diameter.

Figure 7.8. Left atrial shortening fraction (± standard error), obtained from a left view, is displayed in function of time.
After termination of fibrillation, atrial diameters and left atrial shortening fraction gradually returned to normal values after 1 to 2 months of SR.

**Invasive blood pressure monitoring**

**Right ventricle (Table 7.4)**

During the induced fibrillation period, right ventricular pressure during atrial contraction (RVₐ), at end-diastole (RVₐₐ₀₃) and peak systolic pressure (RVₐₘₐₓ) showed a decrease at day 30 but was not significantly altered at day 180. Right ventricular maximal dP/dt was significantly decreased at day 180.

**Right atrium (Table 7.4)**

As a result of AF, right atrial pressure prior to atrial contraction (RAₚ), at the c-wave (RAₙₜₜₚₜ.related.content) and at the v-wave (RAₙₜₜₜ) showed an increased pressure although the increase did not reach significance. AF resulted in a significant decrease in the atrial pressure during atrial contraction (RAₐₚₜₚₜ) and in the maximal dP/dt during atrial contraction (RA_dP/dt). Calculation of the pressure difference produced by atrial contraction showed a significant decrease during the AF period.

**AF duration**

Although an increase in AF duration was associated with shorter AERP values, AERP had to drop below a critical value of about 258 ms before AF paroxysms could persist for more than an hour (Fig. 7.9). Above this value, shortening of AERP was not associated with an increase in AF duration. Yet, below an AERP of 258 ms, association between AERP and AF duration remained rather poor.
Table 7.4. Right atrial and right ventricular pressure recordings (mm Hg) and dP/dt (mm Hg/s), measured during regular atrial pacing at 75 bpm.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>AF period</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>30</td>
<td>180</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>a</td>
<td>14,7</td>
<td>10,3*</td>
</tr>
<tr>
<td></td>
<td>diast</td>
<td>13,7</td>
<td>10,0*</td>
</tr>
<tr>
<td></td>
<td>syst</td>
<td>47,6</td>
<td>43,0*</td>
</tr>
<tr>
<td></td>
<td>dP/dt</td>
<td>544</td>
<td>485</td>
</tr>
<tr>
<td>Right atrium</td>
<td>p</td>
<td>5,0</td>
<td>5,4</td>
</tr>
<tr>
<td></td>
<td>a-wave</td>
<td>8,2</td>
<td>5,5*</td>
</tr>
<tr>
<td></td>
<td>c-wave</td>
<td>4,6</td>
<td>5,2</td>
</tr>
<tr>
<td></td>
<td>v-wave</td>
<td>4,9</td>
<td>5,3</td>
</tr>
<tr>
<td></td>
<td>pressure difference</td>
<td>3,2</td>
<td>0,1*</td>
</tr>
<tr>
<td></td>
<td>dP/dt</td>
<td>57,6</td>
<td>36,4*</td>
</tr>
</tbody>
</table>

a: measurement during atrial contraction; p: measurement at the onset of the P wave
(*: significantly different from control value p< 0.05)

Figure 7.9. Comparison of AF duration and AERP measurements performed at a driving CL of 600 ms.

Figure 7.10. For each pony, AF duration is displayed versus AFCL.
Pony 4 hardly showed any change in AERP although this was the animal with the longest AF duration, requiring defibrillation. In pony 2, longest AF paroxysms were not associated with shortest AERP values.

Figure 7.10 compares AF duration and AFCL. As long as AFCL was longer than 215 ms, AFCL and AF duration were not associated and AF paroxysms remained short. Once AFCL further decreased below 215 ms as a result of repeated AF induction, a decrease of AFCL was associated with an increase in AF duration, and paroxysms of more than an hour could be induced. Sustained AF was only seen in pony 4 at an AFCL of 182 ms. In this animal AF became persistent at an AFCL of 153. Although in pony 3 AFCL shortens below 158 ms, paroxysms in this animal were short.

The animals' height and atrial size importantly influenced AF duration. Largest animals, showing the largest left atrial diameter at baseline, reached the longest AF duration during the study. In Figure 7.11, for each animal, left atrial diameter at the onset of atrial contraction (LADp) obtained from a left view, is shown from baseline until day 180. An atrial diameter of less than 8.2 cm was associated with short paroxysms of AF (< 60 min). When atrial diameter exceeded this critical value as a result of maintained AF, atrial diameter was related to AF duration. Pony 3, with the smallest left
atrial diameter throughout the study, showed the shortest AF paroxysms. In pony 4, with the largest atrial size at the end of the fibrillation period, SR did not restore spontaneously and in this animal defibrillation was required.

**Recovery phase**

As described above, all variables from electrophysiology, echocardiography and blood pressure returned towards normal within 2 months after restoration of SR. While electrophysiological values returned to normal within 10 days, atrial size and atrial contractile function gradually normalized over 1 to 2 months of time. AF duration decreased abruptly to less than a minute within 10 days after restoration of SR, although at that time atrial dilatation was still present (Fig. 7.12).

**Figure 7.12.** Comparison of mean AF cycle length (AFCL), left atrial diameter (left view, pacing rate 60 bpm) and AF duration during the recovery phase. Ten days after cardioversion, AF duration is less than a minute although left atrial diameter has only slightly decreased. (Exact values for AF duration are not displayed because of the individual variation.)
DISCUSSION

In the present study AF was maintained during 6 months in healthy ponies by applying burst pacing. AF resulted in a fast decrease in AERP and AERP rate-adaptation. Consequently, AFCL shortened and the atrial electrogram became more complex. A fast loss of atrial contractile function was observed, which resulted in an increased atrial pressure and a decreased ventricular function. Subsequently, a slow increase in atrial size occurred. As a result of these AF-induced electrophysiological and morphological alterations a progressive increase in AF duration was seen during the 6-month AF period. After restoration of sinus rhythm, all variables returned to normal. Electrophysiological changes and AF duration showed a short time course for normalization, while echocardiographic values needed 1 to 2 months to recover.

Study protocol

This model proved to be efficient to induce and maintain long-term atrial fibrillation in healthy ponies. Implantation of a pacemaker allowed to perform programmed electrical stimulation in order to study atrial electrophysiologic characteristics. Type and rate of fibrillation could be determined from atrial electrogram recordings. Because the model required a minimally invasive implantation technique, reliable blood pressure recordings and echocardiographic studies could be carried out.

Horses with naturally occurring AF mostly are presented with subacute or chronic AF. Therefore, to mimic more closely the natural state of the disease, we developed an equine model in which AF was maintained over a prolonged period of time by permanent implantation of an electrical pulse generator.
Many AF studies have been performed during anaesthesia, in opened-chest animals or in animals with induced pericarditis and these conditions are likely to have an important impact on cardiac function. A major advantage of the closed-chest pony model was that invasive surgery was avoided, thereby preserving normal cardiac function and allowing reliable blood pressure measurements and cardiac ultrasound to be performed. During the whole study, all measurements were performed in the conscious, unsedated animal, thereby avoiding any drug-related interference.

It is known that AF is favoured by underlying cardiac pathology. Valvular insufficiency might cause atrial stretch and atrial dilatation leading to increased susceptibility and perpetuation of AF (Morillo et al., 1995; Allessie, 1998; Power et al., 1998). Local disorders of the myocardium, such as fibrosis, are known promoters of AF (Allessie et al., 2001). In humans, increasing age is strongly associated with an increased risk for atrial fibrillation. A survey in horses also demonstrated increased incidence of AF in aged animals (Else and Holmes, 1971). However, in many horses it is suggested that lone atrial fibrillation is present because cardiac ultrasound reveals no abnormalities or because the animals respond well to quinidine treatment and because they return to their previous level of exercise. It should be mentioned, however, that response to treatment and regaining athletic ability after cardioversion of AF not necessarily indicates absence of underlying cardiac pathology. Moreover, our present diagnostic facilities might be insufficient to detect distinct atrial pathology.

The purpose of our research was to study lone AF in equines. Therefore, young and healthy animals were selected. These animals did not show any abnormalities on cardiologic examinations and were considered to be free of myocardial lesions. Subsequently, by artificial induction and long-term maintenance of AF in healthy subjects, any observed changes would be induced, simply and solely by the
arrhythmia, and would not be confounded by any other cardiac pathology.

Although AF rarely occurs in ponies and is predominantly seen in mature horses (Else and Holmes, 1971; Bertone and Wingfield, 1987; Detweiler, 1989), we used ponies in our study. In a previous report we demonstrated that sustained AF could be successfully induced in the pony heart (van Loon et al., 2000). We suggested that spontaneous restoration of SR after long-term AF maintenance would occur more easily in ponies than in horses, which would be advantageous because during the 6-month AF period, spontaneous restoration of SR was required to perform measurements. Besides, during preliminary research we validated non-invasive echocardiographic cardiac output determination using the well-documented thermodilution technique (Blissitt et al., 1997), which could be performed more easily in smaller sized animals (unpublished data).

AF is characterised by an irregularly irregular ventricular rate. As differences in diastolic times result in different preload and afterload conditions, important alterations in cardiac function occur, and confusing results might be found during AF (Leistad et al., 1993a; Leistad et al., 1993b; Hardman et al., 1998). In the present study, echocardiography and blood pressure recordings were performed after spontaneous reversion of sinus rhythm, and during regular atrial pacing. Subsequently, confounding effects of ventricular arrhythmia or changes in heart rate that might occur during the study were eliminated. The reason why a pacing rate of 75 bpm was chosen to perform blood pressure measurement and cardiac ultrasound was that some animals showed a SR of about 60 bpm during the study. To be sure that consistent atrial pacing occurred at any time, a rate of 75 bpm was chosen to perform ultrasound and blood pressure measurements. However, at this rate, rapid ventricular filling phase in early diastole and atrial contraction were not clearly distinguishable. Consequently, left atrial diameter before initiation of atrial contraction
(LAD$_p$) could not be determined accurately at 75 bpm, which made calculation of left atrial shortening fraction impossible. Additional left atrial measurements were therefore performed at a pacing rate of 60 bpm.

In other animal models, induction of AF is often associated with an important increase in ventricular rate. When subsequently, alterations in electrophysiological properties, or in atrial or ventricular structure and function, are found, these might be biased by the ventricular rate or by ventricular tachycardiomyopathy. In the present study, heart rate during AF was only slightly higher than during SR and was unlikely to affect experimental results.

**Electrophysiologic changes induced by AF**

In animals, contrasting results about the effect of AF on sinus node function have been reported. While in the isolated rabbit heart, during atrial fibrillation, sinus automaticity was still present in the centre of the sinus node and hardly overdrive suppressed due to a high degree of sinoatrial entrance block (Kirchhof and Allessie, 1992), in dogs, 2 to 6 weeks of maintained AF caused an impaired sinus node function (Elvan et al., 1996), confirmed by a prolongation of cSNRT. Also in humans, chronic AF can be associated with a depressed sinus node function (Manios et al., 2001). In our ponies, no significant changes in SNRT or cSNRT could be demonstrated after 6 months of AF. This could be partly explained by the technique for SNRT measurement in the present study. While in human medicine it is generally accepted that SNRT should be determined with an electrode that is positioned near to the sinus node (Fogoros, 1995), the exact position of the implanted atrial electrode in relation to the sinus node was not known. Electrode position too far away from the sinus node might have influenced our results. However, in each animal the permanently implanted electrode remained in the same position during the whole study, suggesting that alterations in sinus node function during the study still might be detected. To the best of our knowledge, information
about SNRT determination in horses is not available in literature. It could be that, because measurements were performed in the conscious ponies, changes in autonomic tone occurred during these measurements, confounding the results. Determination of SNRT after autonomic blockade with propranolol and atropine might have provided more conclusive results.

As a result of prolonged pacing-induced AF, the previously normal atrium now maintained longer paroxysms of AF. The increased AF duration might be explained, at least in part, by the shortening in AERP. Because the length of a reentry wavelet is defined as the product of AERP and conduction velocity, AERP shortening resulted in a shortening of the wavelength. According to Moe’s multiple wavelet hypothesis (Moe, 1962), a long wavelet may not permit reentry to sustain, causing fibrillation to terminate, whereas a short wavelength allows multiple wavelets to coexist in the atria, thereby favouring AF persistence. Although atrial conduction velocity could not be measured in this study, it presumably remained similar or even decreased as a result of AF, as it was shown in other species (Morillo et al., 1995; Wijffels et al., 1995; Elvan et al., 1996).

It has been reported that in human patients a poor or absent rate adaptation of the AERP might be the cause of AF (Attuel et al., 1982; Boutjdir et al., 1986). Normal ponies used in the present study showed an adaptation of AERP to rate, which was attenuated by pacing-induced AF. After cardioversion to SR the normal adaptation to changes in heart rate was restored within 10 days. The present observations thus suggest that maladaptation of AERP is rather the result of AF than the cause of it.

Repeated AF induction resulted in a faster rate of fibrillation as evidenced by the decreased AFCL. Previous studies have demonstrated a high correlation between local fibrillation interval and refractory period (Wijffels et al., 1995). In that case AFCL could be used as an index for AERP estimation. Such an index would be
advantageous as it could be applied during AF and make restoration of SR during the study redundant. However, median fibrillation interval is not equal to local refractory period as during AF a small excitable gap is still present (Allessie et al., 1991; Kirchhof et al., 1993; Duytschaever et al., 2001).

**AF-induced changes in atrial size and function**

In our study, atrial diameters were measured rather close to the mitral valve annulus because apical views cannot be obtained in horses. Measurements of atrial area obtained from apical views more closely reflect true atrial size and might provide a higher sensitivity in exposing subtle changes in atrial dimension. However, in our study a significant gradual increase in atrial size could be demonstrated as a result of atrial fibrillation. It should be emphasized that we did not perform echocardiography during a fibrillating rhythm but during regular atrial pacing. Measurements of atrial size during AF are not only confounded by the irregular ventricular rate but also by decreased atrial compliance that reduces atrial diameter (White et al., 1982; Leistad et al., 1993a). The decreased compliance during AF is caused by the unsynchronised, continuous muscle fibre contractions, by higher intracellular calcium concentrations in atrial fibres during the noncontracting phase, or by a greater myocardial turgor due to an increase in atrial blood flow during fibrillation (Leistad et al., 1993a). The AF-induced increase in atrial size was suggested to be partly caused by an increase in atrial pressure (Oldham et al., 1967; White et al., 1982; Leistad et al., 1993a). In the present study, increase in atrial pressure did not reach statistical significance. The reason why atrial diameters changed significantly while pressure differences were less obvious, could be the limited number of animals, but could also be explained by the fact that pressures were measured in the right atrium while diameters were measured in the left atrium. It has been shown in other animals that AF-induced changes in pressure and size are less pronounced in the right heart compared to the left heart (White et al.,
In our study, pressures were measured in the right heart because left atrial catheterisation using a high-fidelity catheter is technically more difficult in horses, and echocardiographic variables were determined for the left heart because reliable echocardiographic landmarks for the right heart are lacking.

As a result of maintained AF, atrial pressure during maximal atrial contraction, the a-wave, was decreased. Although this could suggest a decreased atrial contractility, a-wave was also influenced by pre- and afterload conditions, and did not reflect atrial contractile function. Therefore, in addition, atrial pressure immediately before the onset of atrial contraction was measured, which allowed calculating the pressure difference generated by atrial contraction. This generated pressure difference was completely abolished by pacing-induced AF, indicating that, even during the short restoration of SR, atrial contractility was almost completely lost. As right atrial a-wave nearly disappeared on the atrial pressure tracings, right atrial maximal dP/dt during atrial contraction was significantly depressed. However, it should be emphasized that maximal dP/dt in the right atrium only indicates the pressure rise generated by atrial contraction and does not provide a true reflection of atrial inotropic state, as the latter only applies for measurements performed during the isovolumetric phase of the contraction (Van den Bos et al., 1973; Brown and Holmes, 1978), a condition that was not full-filled in the atrium.

Left atrial contractions are difficult to visualize on echocardiography (Wingfield et al., 1980) and M-mode analysis of mitral valve movement has been used as an attractive alternative in visualising the effects of AF in horses. However, mitral valve movement is highly affected by atrial and ventricular loading conditions and thus poorly reflects atrial inotropic state. To the best of our knowledge, real estimation of atrial contractility in equines has not been reported in literature. In equine literature, ultrasonographic estimation of atrial size is generally performed at the end of ventricular diastole and systole, but does not
allow evaluation of atrial contractile function. In the present study, we introduced additional left atrial measurements at different timings during the cardiac cycle to estimate atrial contractility. By determining atrial diameter immediately prior to atrial contraction and again during maximal atrial contraction, shortening fraction of the left atrium was calculated by adapting the well-documented formula for left ventricular shortening fraction (Feigenbaum, 1986). The index proved to be sensitive in detecting changes in atrial inotropic state non-invasively. Ten days of AF already reduced left atrial shortening fraction from 16.5% at baseline to 2.1%. After 6 months of AF a nadir of –0.5% was reached. The negative value of atrial fractional shortening indicates that passive atrial filling resulted in an increase in atrial diameter, even though the atrium was contracting maximally.

**Effect of AF on the ventricle**

Similar remarks as for the atria can be given concerning pressure measurement performed in the right ventricle and ultrasound completed on the left ventricle.

A decreased diastolic ventricular diameter and area indicated an incomplete left ventricular filling caused by a loss of atrial contraction. By the Frank-Starling mechanism, the decreased ventricular preload resulted in a reduced inotropy, which was evidenced by the increased systolic diameter and area, and concomitant decreased fractional shortening and fractional area change, and also the reduced right ventricular maximal dP/dt. The depressed ventricular performance subsequently resulted in a lower ventricular peak pressure and a reduced aortic flow velocity. The final result was an obvious decrease in stroke volume and thus cardiac output. An AF episode as short as 10 days was already sufficient to result in a significantly reduced ventricular performance. As ventricular rate during pacing-induced fibrillation was not markedly increased during our study, occurrence of ventricular tachycardiomyopathy could be prevented and reduced.
ventricular function was predominantly attributed to the decreased preload.

Other studies in equines described contradictory results concerning cardiac output. Muir et al. (1984) reported normal cardiac output values measured during AF in 7 horses with naturally occurring AF, provided that they didn’t show signs of congestive heart failure. In 4 of these horses, cardiac output was again measured after restoration of sinus rhythm. After cardioversion an increase in output was observed in one animal, while no changes were detected in the remaining 3 horses. However, in none of these horses the duration of fibrillation was known. Furthermore, it remained unclear to what extent quinidine treatment, influenced hemodynamic results. In 1975, Kubo et al. investigated the effect of experimentally induced short-term AF paroxysms on cardiac output in 7 healthy horses. Compared to SR, they found increases as well as decreases in cardiac output after experimental AF induction. On the average, cardiac output increased by 12%, which turned out to be not significant. However, a significant increase in heart rate of 43% was observed, resulting in a significant decrease in stroke volume (22%). It should be stressed that in both above-mentioned reports measurements were performed during AF. Consequently, hemodynamic alterations are the result of multiple factors such as reduced atrial compliance during AF, AF-induced depressed atrial contractility, irregular ventricular rhythm and different ventricular rate.

**Reversibility of AF-induced changes**

Although AF resulted in important changes in atrial electrophysiology, size and function, all these changes appeared to be reversible within 2 months after restoration of sinus rhythm. A short time-course was observed for the electrophysiologic changes, normalizing within 10 days after cardioversion. Atrial size and contractility, and concomitant left ventricular function, needed 1 to 2 months to recover after the 6 month AF period. These results are in
agreement with the findings of Allessie (1998) who suggested that metabolic changes, such as differences in ion concentrations or in ion pump activities, occurred and disappeared within seconds to minutes, while changes in electrical remodeling needed hours or days. Many studies reported a postfibrillatory atrial contractile dysfunction, requiring weeks to months to recover (Jordaens et al., 1993; Van Gelder et al., 1993; Manning et al., 1994; Allessie, 1998; Schotten et al., 2001). Cellular mechanisms responsible for AF-induced contractile dysfunction are still poorly understood. Alterations in atrial cellular ultrastructure and a reduction in L-type Ca$^{2+}$ current have been suggested as plausible mechanisms (Ausma et al., 1997; Yue et al., 1997; Bosch et al., 1999; Van Wagoner et al., 1999; Schotten et al., 2001).

**What can we conclude about AF duration?**

Immediately after induction of AF, the AFCL started to shorten. Initially, the decrease in AFCL was not accompanied by an increase in AF duration. Only when AFCL had shortened to a critical value, AF duration started to increase. Similarly, only after an increase in atrial size above a critical value, AF paroxysms progressively increased. These findings are in agreement with the multiple wavelet hypothesis (Moe, 1962). Because of the shorter atrial refractoriness, and concomitant shorter wavelength and fibrillation CL, and because of the increase in atrial diameter, a larger number of wavelets wander around in the atria, decreasing the statistical probability of simultaneous extinction and favouring AF perpetuation. In the isolated Langendorff-perfused canine hearts, the critical number of wandering wavelets for perpetuation of fibrillation was between 3 and 6 (Allessie et al., 1985). The lifetime of individual wavelets was very short, about a few hundred milliseconds. Continuously, ‘old’ wavelets extinguished by fusion or collision with another wavelet, by reaching the border of the atrium, and because the advancing depolarisation wave met an area where the myocardium had not recovered its excitability from a foregoing
activation. At the same time new wavelets were formed by division of 
an existing wave at an area of conduction block, an offspring 
traversing toward the other atrium, and possible sources of impulse 
formation. The approximate number of atrial wavelets during AF 
can be determined during mapping studies or can be estimated when 
conduction velocity, refractory period and atrial size are known. 
However, studies in dogs have shown a spatial dispersion and 
temporal inhomogeneity in AERP and, in addition, conduction velocity 
during AF was shown to vary from 20 to 139 cm per second in the 
same animal, resulting in a continuously changing wavelength and a 
varying number of wavelets (Allessie et al., 1994).

Both a decrease in AFCL and an increase in atrial diameter 
appeared to be required in order for AF to become sustained. In dogs, 
a minimal reduction of 15% in AERP associated with an increase of at 
least 40% in atrial area was highly predictive of sustained AF (Morillo 
et al., 1995). This also explains the abrupt reduction in AF duration 
during the recovery period: although after restoration of SR, initially, 
atrial diameter had barely changed, the fast occurring increase in 
AERP and AFCL toward normal values, prevented AF to perpetuate. 
With these findings we can explain why naturally occurring AF is never 
seen in ponies: their atrial electrophysiological properties and their 
atrial size simply prevent sufficient wavelets to coexist in the atria. 
Surprisingly, after pacing-induced electrical and morphological 
remodeling, long-term AF could be induced in ponies.

**Clinical implications**

In equine medicine it is believed that AF often is present as ‘lone’ 
AF, i.e. without overt underlying heart disease. However, very little 
information is available on the initiation of AF, and what AF actually 
does in a healthy animal. The present model demonstrated the 
feasibility of developing a reproducible model of long-term AF in 
healthy equines to expand our understanding of the mechanisms
leading to AF. In the future, this model will facilitate the development of different therapeutic modalities in horses.

In the present study adapted left atrial measurements were introduced in order to establish atrial contractile function non-invasively. Such an index could be applied to reveal atrial disease in equines. Especially after cardioversion of AF, calculation of atrial shortening fraction is useful to assess restoration of atrial contractile function.

The results of this study indicate that, after initiation of atrial fibrillation, changes in electrophysiological parameters develop fast to reach a plateau, and that they return quickly to normal after restoration of SR. Dilatation of the left atrium appears slower and continues to progress over a longer period of time, normalizing again about 2 months after cardioversion. Therefore, it is suggested that after successful treatment of chronic atrial fibrillation, training should only be resumed after a period of about 1 to 2 months, i.e. after restitution of atrial electrophysiologic characteristics, atrial contractile function and atrial diameter. As atrial diameter seems to be an important predictor, not only for AF stability but also for successful restoration of SR and for the risk of AF recurrence, the atrial diameter is often determined prior to initiation of AF therapy, where horses with a dilated left atrium are given an unfavourable prognosis. As in the present study, AF-induced atrial dilatation occurred in normal individuals, this parameter should be interpreted cautiously in chronic fibrillating animals without valvular disease. A long-term follow-up of animals with a normal left atrial diameter and recent onset lone AF should be performed to provide more information about changes in left atrial diameter in horses with naturally occurring AF. Furthermore, little information is currently available about the correlation between left atrial diameters measured during SR and during AF. The present model could be applied to study this relationship.
At present, little is known about the effect of high-level performance on the inducibility or persistence of AF. During high performance, cardiac load may be higher and this might affect atrial pressure, diameter and stretch, which might be important factors explaining AF susceptibility (Leistad et al., 1993a; Morillo et al., 1995; Sideris et al., 1995). The time-course of the occurrence of electrophysiologic, pressure or echocardiographic alterations might therefore differ in horses that remain in training.

As mostly seen in lone AF horses, AF-induced tachycardia at rest did not develop during the present study. The high vagal tone in equines results in a high degree of concealed conduction at the AV node. This confirms that in horses with lone atrial fibrillation rate control is not required and only rhythm control has to be considered.

In humans, AF is associated with an increased risk of systemic thromboembolic complications, particularly strokes, although it has been reported that the risk would not be increased in patients with lone AF (Kopecky et al., 1987; Elvan et al., 1999). In the present study, during echocardiographic examinations special attention was paid to the presence of atrial thrombi, but none could be identified. Also in clinical cases thromboembolic events are not reported and seem to be negligible in horses, making anticoagulation therapy redundant.

In human medicine, antiarrhythmic therapy is generally continued after restoration of SR to prevent early recurrence of AF. One of the possible explanations for the high incidence of early recurrence of AF could be the inversed rate adaptation curve of the AERP that can occur. When inversed rate adaptation is present, restoration of SR implies a decreased atrial rate and thus a shortening of the refractory period instead of an increase. The shorter refractory period again favours AF occurrence. As a reversed rate adaptation was not seen during our study, this might be a contributing factor for the low incidence of early AF recurrence seen in equines and might therefore
suggest that antiarrhythmic therapy after successful restoration of SR is not required in this species.

**Limitations of the study**

In the present study only 4 animals were implanted and followed during the 6-month AF period. Due to the limited number of animals, the results and statistical analyses must be interpreted cautiously. However, most variables altered similarly in all animals, suggesting that valuable conclusions could be drawn.

Pacemaker output was set at 2 times diastolic threshold. In some studies, a stimulation output of 4 times threshold was used, yielding a more aggressive pacing protocol for AF induction. Furthermore, during our study, SR detection appeared during 3 to 4 consecutive sinus beats. As the resting sinus cycle length in the ponies was about 1200 to 1500 ms, each SR episode persisted for about 4 to 6 seconds before AF was re-induced. As electrical reversed remodeling appeared fast, this short period of SR detection might have influenced induction and perpetuation of AF. Measurements of electrical parameters, echocardiography and blood pressures were performed after spontaneous reversion of SR. These periods of SR also might have influenced the experimental results.

One atrial electrode was used for determination of electrophysiologic properties. It is known that, at a certain point in time, AERP and AFCL vary among the location in the atrium (spatial dispersion). In addition, a local area may show different AERP and AFCL values in time (temporal dispersion). Therefore, multiple electrodes are desirable to make detailed electrophysiological measurements. However, a continuing problem exists with chronic AF models in achieving a balance between the area from which information is gathered by electrode implantation and any effects of the implantation per se, which may be related to the epicardial area in contact with the electrodes (Power et al., 1998).
From this study we can conclude that, in healthy equines, AF induces changes in electrophysiological properties that lead to AF perpetuations. Furthermore, six months of maintained AF results in atrial dilatation and atrial contractile dysfunction, which needs 1 to 2 months to recover after cardioversion. All AF-induced changes were fully reversible.

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This thesis shows that temporary and permanent pacing can be readily achieved in equines opening new perspectives to diagnose, treat and understand equine dysrhythmias. Temporary atrial pacing cannot be applied to terminate atrial fibrillation (AF) (Allessie et al., 1994), but it can successfully entrain and interrupt atrial flutter (Kantharia and Mookherjee, 1995; Osborn, 1996). Atrial flutter sometimes occurs as intermediate rhythm during quinidine treatment in AF horses (Betsch, 1991; Matsuda, 1992; van Loon et al., 1998). Because of the vagolytic action of quinidine and its ability to slow flutter rate, quinidine therapy facilitates atrioventricular (AV) conduction and occasionally results in a 1:1 ventricular response to atrial flutter, initiating ventricular tachycardia or even ventricular fibrillation (Fregin, 1982; Zipes, 1992). This could be a possible explanation for the death of some horses during quinidine therapy (Brooijmans, 1957; Deem and Fregin, 1982; Betsch, 1991). In this context, overdrive pacing might well be an aid in the treatment in AF. It is well known that quinidine has a narrow therapeutic index (Bouckaert et al., 1994). During AF treatment in horses, the quinidine plasma level is progressively increased toward therapeutic but also toxic levels. In case atrial flutter would occur during the quinidine treatment, overdrive pacing could be applied to terminate atrial flutter. As such, conversion to sinus rhythm might be achieved earlier during the AF treatment, reducing the quinidine dose and thereby the risk of lethal arrhythmias or other toxic side effects.

The presence of atrial flutter or atrial fibrillation is not always identifiable on a surface ECG. The use of a temporary pacing catheter allows distinguishing between AF and atrial flutter, and determining AF type and AF cycle length (Gallagher and Camm, 1998; van Loon et al., 1998). The temporary pacing technique can be applied for further research in normal horses and horses with AF in order to determine atrial electrophysiological characteristics, such as sinus node recovery time, atrial effective refractory period and rate adaptation of atrial refractoriness, and in order to develop pacing protocols for estimating
atrial vulnerability for AF. The latter would be useful in horses suspected of having paroxysmal AF during high performance and in horses treated for AF in order to estimate the risk for relapse into fibrillation.

Permanent pacemaker implantation expands our ability to treat equine rhythm disturbances. Nowadays, refurbished pacemakers intended for veterinary use only, are available and reduce the cost of the device. This thesis describes a transvenous implantation technique that is applicable for implantation of single chamber as well as dual chamber pacemakers, with or without rate-responsiveness. Consequently, the pacemaker type that best meets the patient’s needs can be selected for implantation.

The simplest implantation is the one of a single chamber model with a ventricular lead. Such a pacemaker could be applied to preserve a minimal ventricular rate in cases of symptomatic bradycardia. Absent AV synchrony, however, results in a loss of atrial contribution to ventricular filling, decreasing ventricular preload and thereby stroke volume (Reynolds, 1996). Because presystolic valve closure is lacking, mitral valve regurgitation may occur early in systole, further reducing cardiac output (Hayes and Osborn, 1996). The ventricular demand pacemaker only ascertains a minimal heart rate and cannot adapt its rate to exercise. The use of a rate-adaptive ventricular pacemaker with a built-in sensor, allows achieving a heart rate that varies in response to exercise.

In patients suffering from sinus node dysfunction but with a normal AV conduction, a single chamber atrial pacemaker could theoretically be applied. But atrial lead displacement is a potential complication of transvenous leads (Sisson, 1989; Sisson et al., 1991; Darke, 1992; Flanders et al., 1999) and such a dislocation would result in loss of pacing. Therefore, symptomatic horses should rather receive a dual chamber pacemaker programmed in dual chamber pacing mode to
preserve ventricular pacing in case atrial lead dislodgement would occur.

Dual chamber models have the capability to perform both pacing and sensing in atrium and ventricle, which is advantageous in a variety of situations. Four different rhythms can be observed as a result of normal dual chamber pacemaker function: (1) normal sinus rhythm, which inhibits atrial and ventricular pacing; (2) atrial pacing as a result of sinus (atrial) bradycardia with intact AV conduction; (3) AV sequential pacing when atrial and ventricular bradycardia exist independently; and (4) atrial synchronous pacing, which occurs in case of heart block with normal atrial (sinus node) activity (Hayes and Osborn, 1996). The latter means that ventricular pacing is performed each time an atrial activity is sensed, thus producing an atrial-triggered adaptation of ventricular rate, for example in response to exercise. This also means that in patients with paroxysmal atrial tachyarrhythmias automatic mode switching to a non-tracking mode must be present to avoid ventricular pacing at the upper rate limit during an inappropriately rapid atrial rhythm (Hayes and Levine, 1996; Provenier et al., 1994; Reynolds, 1996). When normal sinus node function is lost, in the presence of chronotropic incompetence, the use of a rate-adaptive pacemaker model is recommended to obtain a heart rate that varies according to physical activity.

Although the main purpose of pacemaker implantation is the treatment of bradycardia, pacemakers have been used in numerous cardiac studies in dogs, pigs, goats and sheep (Morillo et al., 1995; Wijffels et al., 1995; Elvan et al., 1996; Yue et al., 1997; Qi et al., 2000; Willems et al., 2000). Indeed, pacemaker programmability and availability of different pacing modalities allow emulating acute or chronic arrhythmias and studying electrophysiologic variables over time. In this thesis pacemakers were used to develop a model for chronic AF in equines. Although AF can be induced by delivering single extrastimuli, preliminary results indicated that AF in ponies could
not be consistently maintained in this way. Pacemaker adaptation with a fibrillation-induction program applying atrial burst pacing was needed to maintain AF continuously. As horses with naturally occurring AF are often only presented after days, weeks or months, a chronic AF model was essential to study AF pathophysiology. A major advantage of the equine model is the non-invasive character, which implies that accurate blood pressure measurements and cardiac ultrasonography can still be performed. Both the absence of iatrogenic cardiac pathology, such as pericarditis, and the normal ventricular rate during AF, make the model an excellent means to study the effects simply and solely induced by AF, without other interfering factors. The equine model may therefore contribute to the understanding of AF and may provide additional information transferable to human cardiology.

During AF, cardiac output is generally decreased (Kubo et al., 1975; Deegen and Buntenkotter, 1976; Wingfield et al., 1980; Deem and Fregin, 1982; Miller and Holmes, 1984; Muir and McGuirk, 1984; Deegen, 1986; Betsch, 1991; Marr et al., 1995). Output is defined by heart rate and stroke volume, and stroke volume depends on the inotropic state of the myocardium and on pre- and afterload conditions. As in equines little or no increase in ventricular rate is seen during AF, ventricular tachycardiomyopathy is unlikely to be the cause of the decreased output. There is also little reason to believe that noticeable differences in afterload, other than the varying diastolic intervals, are present. A decreased cardiac output can therefore be attributed to changes in heart rate and, by the Frank-Starling mechanism, to an altered ventricular filling. AF results in an irregular ventricular rate and in consequence in varying diastolic intervals that alter ventricular filling and thereby stroke volume (Miller and Holmes, 1984; Prystowsky et al., 1996). First, regardless of irregular heart rate, ventricular filling is reduced by a decreased atrial emptying. During AF, waves of excitation circle continuously around the atria causing independent contraction of individual muscle fibres rather than a synchronous contraction of the atria. Consequently, the atria fail to contract as a
whole and ventricular filling, and thereby stroke volume, is reduced (Kubo et al., 1975; Blissitt, 1999). Secondly, the inotropic state of the atrial myocardium might play a role in the reduced ventricular filling. In order to estimate the importance of atrial contractile function per se, not biased by the irregular atrial and ventricular activity, measurements at a regularly paced rhythm were performed. During the maintained fibrillation period this could be achieved after spontaneous restoration of sinus rhythm. It was shown that not only chaotic atrial and ventricular rhythm but also atrial contractile dysfunction importantly contributes to the depressed ventricular function. In this study, atrial contractile function was estimated by intra-atrial pressure measurements, but, in addition, adapted echocardiographic variables were introduced to establish atrial contractility non-invasively. It should be mentioned that due to technical limitations, atrial diameter was measured not at the largest atrial cross-section but rather close to the mitral valve annulus, possibly reducing the sensitivity of the variables. However, atrial shortening fraction showed a highly significant decrease, even after a short AF episode, suggesting that it is a valuable means to estimate atrial contractile function in clinical patients. A last factor influencing cardiac output is AV valve function. Under normal conditions, atrial contraction increases ventricular pressure sufficiently during early atrial diastole to reverse the AV pressure gradient, thus placing the AV valve leaflets in approximation before or at the onset of ventricular systole (Hayes and Osborn, 1996). Deficient atrial contraction prevents presystolic AV valve closure. As a result, further reduction of stroke volume may occur due to AV valve regurgitation (Holmes et al., 1969; Leistad et al., 1993). In humans, however, this kind of AV valve incompetence is thought to be of negligible importance and in the pony model no evidence of significant AV valve regurgitation could be observed on colour flow Doppler.

In horses with AF, loss of performance is the major clinical sign (Bertone and Wingfield, 1987; Reef et al., 1988; Reef et al., 1995; Mitten, 1996). The decreased athletic ability is predominantly ascribed
to a reduced cardiac output caused by an insufficient ventricular filling. At rest, passive ventricular filling and compensatory mechanisms are mostly sufficient to retain cardiac output. During exercise, atrial contribution to ventricular preload becomes increasingly important. Under normal circumstances, atrial contraction is reported to contribute up to 20 to 30% in the filling of the ventricles (Brooijmans, 1957; Nolan et al., 1969; Hayes and Osborn, 1996). During AF, ventricular filling is not only altered by the irregular rhythm but also by the reduced atrial contraction. Because of the atrial contractile dysfunction and possibly AV valve regurgitation (Leistad et al., 1993) atrial pressure rises. Consequently, venous return is reduced and systemic and pulmonary venous congestion might occur. Especially during exercise, left atrial hypertension may arise and cause exercise-induced epistaxis associated with some cases of AF (Deem and Fregin, 1982). Left atrial hypertension may also lead to the occurrence of lung oedema, which hampers oxygen exchange and further reduces performance. Although in equine literature little attention is paid to the influence of heart rate, this should not be underestimated. From literature data and clinical observations it is known that, even during slight efforts, heart rate in the AF horse increases disproportionately to work (Deegen and Buntenkotter, 1976; Steel et al., 1976; Maier-Bock and Ehrlein, 1978). In part, this tachycardia might be a compensatory mechanism for the decreased cardiac output. However, tachycardia is often excessive, which might have a negative effect on cardiac output due to the short diastolic intervals, hampering ventricular filling, especially in the absence of atrial contribution (Miller and Holmes, 1984). AF-related tachycardia could also be attributed to a change in autonomic tone. Unless underlying cardiac pathology is present, ventricular rate in the resting horse with atrial fibrillation is normal because of a high degree of concealed conduction, caused by the high vagal tone and the size of the AV node (Meijler and van der Tweel, 1987; Meijler, 1990; Prystowsky et al., 1996; Kuwahara et al., 1998). In contrast, increased resting heart rates are often associated with AF in
man and dogs (Ruffy, 1995; Prystowsky et al., 1996). During moderate exercise, the decreased vagal tone and the predominance of the sympathetic tone reduce the concealed conduction (Prystowsky et al., 1996). Many atrial depolarisation waves are suddenly conducted through the AV node and a disproportionately high ventricular rate is observed.

To be maintained, AF requires a critical number of wavelets simultaneously present in the atria (Allessie et al., 1985). A large number of wavelets can coexist when the atria are large, the conduction velocity is slow and the refractory period is short, and additionally, when there is heterogeneity in conduction velocity and refactororiness (Wijffels et al., 1995; Zipes, 1997; Allessie, 1998). In horses, AF is favoured both by the large atrial mass and the high vagal tone. A high vagal tone shortens the refractory period of individual cells to a varying degree and consequently causes differences in the length and phase of the action potential (Moe, 1962; Bertone and Wingfield, 1987; Moore and Spear, 1987; Liu and Nattel, 1997; Wijffels et al., 1997; Zipes, 1997; Blissitt, 1999). In addition, some authors suggest that in large mammals (such as horses), wavelength of the atrial impulse does not increase proportionally to the size of the atria (Allessie et al., 1990). Horses are so vulnerable to AF that most of the AF horses don’t need any underlying cardiac pathology to develop the disease but present the so-called lone AF (Fregin, 1971; Rose and Davis, 1977; Amada and Kurita, 1978; Deem and Fregin, 1982; Reef et al., 1988; Detweiler, 1989; Collatos, 1995). In the study of Reef et al. (1988), almost 60% of the horses with AF were diagnosed to suffer from lone AF. The high occurrence of lone AF in horses could be supported by the high vagal tone. In man, it is known that lone fibrillators often present attacks during predominant parasympathetic stimulation (Huang et al., 1998), while paroxysms in patients with structural heart disease more frequently occur in a sympathetic setting (Allessie et al., 2001). Horses are diagnosed of having lone AF when no cardiac disease other than AF is found during examinations, or
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when they respond well to quinidine treatment and are able to return to work after successful cardioversion (Deem and Fregin, 1982; Reef et al., 1988; Detweiler, 1989). It should be stressed, however, that lone AF is AF without evidence of other cardiac or systemic disease known to promote AF (Evans and Swann, 1954), and like any diagnosis of exclusion, its quality varies according to how rigorously one searches for an alternative (Gallagher and Camm, 1998). In a series of 230 human patients referred to a specialized AF clinic, all were found to have some predisposing condition (Hurst et al., 1964). A more recent study in man evidenced that all patients with lone AF presented abnormal atrial histology (Frustaci et al., 1997). Literature data describing atrial pathology in normal horses and horses with AF are limited. In a survey of 45 horses with AF, post-mortem examination of the atria revealed both macroscopic changes, such as dilatation, and microscopic lesions, such as fibrosis (Else and Holmes, 1971). Overexertion and strain were suggested to belong to the possible mechanisms leading to these atrial lesions. In another study, histopathological examination on 2 AF horses revealed myocardial fibrosis in both of them (Kiryu et al., 1974). In a study on 19 horses without arrhythmias, however, 4 normal animals also presented focal fibrosis in the atrial myocardium (Kiryu et al., 1981). The precise importance of such lesions in the occurrence of AF therefore still remains uncertain (Bertone and Wingfield, 1987). In horses, successfully treated for ‘lone’ AF, recurrence rates of 25% have been reported (Reef et al., 1995). It should be noticed that these animals might present distinct microscopic lesions that were not diagnosed. Besides, recurrence of AF is said to be more likely in horses that are brought back into training (Glendinning, 1965; Kroneman and Breukink, 1966). This could be explained by exercise-related changes in heart rate and autonomic tone. Additionally, during exercise, increase in atrial pressure is significantly higher in horses than in other species (Manohar et al., 1994). Consequently, a higher increase in atrial diameter and stretch is to be expected, which is known to have
profibrillatory effects (Zipes, 1997; Allessie, 1998; Janse et al., 1998; Franz, 2000). As a result, electrical remodeling, increase in AF duration, atrial dilatation and atrial contractile dysfunction might be more pronounced or show a different time course when the animals continue high-level performance.

Apart from the influence of atrial lesions on AF occurrence, it has been shown in other animal models that AF itself also induces changes in atrial structure, such as myolysis, fragmentation of sarcoplasmatic reticulum, and loss of myofibrils. (Morillo et al., 1995; Ausma et al., 1997a; Ausma et al., 1997b; Thijssen et al., 2000). To what extent structural remodeling occurs in horses with AF is yet unknown.

As induced fibrillation in ponies results in electrical remodeling and atrial dilatation further leading to AF perpetuation, the present work supports the concept of ‘AF begets AF’ (Wijffels et al., 1995). These findings explain why animals with longstanding AF are more difficult to convert to SR (Deem and Fregin, 1982; Reef et al., 1988; Reef et al., 1995). However, research in horses will have to prove whether or not AF leads to a similar atrial dilatation as in ponies, because thickness of the atrial wall might play a role in occurrence of dilatation.

Future research should focus on the question whether horses actually present ‘lone’ fibrillation and whether AF occurrence or recurrence is predictable in an individual horse. Ultrasonography and estimation of atrial contractile function might help identifying animals with overt atrial fibrosis. In cardioverted horses atrial contractile function should be restored before training is recommenced. If proper restoration is not observed an underlying atrial disease might be present and relapse of AF could be more likely. In this thesis it was shown that atrial size importantly contributes to AF perpetuation. In the pony model, a difference in atrial diameter of 1 cm resulted in an obvious increase in AF duration. In horses, reference values for atrial diameter show a large variation. Slight increases in atrial diameter, as
observed in the pony model for AF, probably would fall within normal limits. It should therefore be attempted to narrow reference values for horses by examining a large number of them and by clearly differentiating between breeds. If horses are presented with AF, echocardiography is always performed prior to the onset of treatment to intercept patients with congestive heart failure. Further studies are also needed to clarify the correlation between atrial diameter measured during SR or measured during AF.

Some animals possibly present a faint balance between atrial size and refractory period, favouring AF occurrence. Application of temporary pacing to perform electrophysiologic studies in a large number of normal horses will permit to compare reference values for refractoriness and adaptation of refractory period with those of AF converted animals. Individual electrophysiological differences might thereby indicate an increased risk for AF. A pacing protocol, adapted to horses, will enable assessment of atrial fibrillation threshold, which will be an additional aid in identifying animals suspected of having paroxysmal AF during strenuous work. The combination of electrophysiologic characteristics and atrial size might provide a predictive value for the likelihood of AF occurrence in an individual animal.

Although in human medicine AF has been intensively studied and has been called the ‘darling arrhythmia’ of the past decade (Zipes, 1997), many questions still remain to be answered. The present pony model affords a glance behind the scenes of AF pathophysiology in equines and could be applied in future to gain further insight into this mystifying arrhythmia.
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SUMMARY

Cardiac pacing has become a mainstay in human cardiology for diagnosis and treatment of many dysrhythmias and has been applied in numerous animal models to study the pathophysiology of rhythm disturbances. In equines, however, little research has been performed concerning rhythm disturbances and in this species diagnostic and therapeutic modalities are limited. Cardiac pacing has hardly been studied in equines, and therefore research on its applicability was tempting, especially to study pathophysiological aspects of atrial fibrillation (AF), clinically the most important arrhythmia in horses.

In this thesis a General introduction discusses general features of atrial pacing and AF. The first part of the introduction gives an overview of physiologic aspects and required equipment to perform pacing. The use of cardiac pacing in man is summarized, discussing therapeutic and diagnostic features. Subsequently, a review is presented of all available literature data on cardiac pacing in equines. Reports describing therapeutic pacing as well as pacing during cardiac studies are briefly discussed. In the second part of the introduction, general electrophysiological aspects on AF are summarized and an overview about knowledge on AF in equines is given. It is obvious that AF results in exercise intolerance. However, the association between AF and pathologic changes such as atrial dilatation, atrial contractile dysfunction, ventricular dysfunction, histological changes and electrophysiologic alterations remains unclear.

The research of the thesis consists of two major sections. The first section (Chapters 1 – 4) describes the development of a technique to perform temporary as well as permanent atrial pacing. Both techniques are applied to treat clinical patients.
In the second section (Chapters 5 - 7) the atrial pacing techniques are applied to develop an equine model for chronic atrial fibrillation. This model was subsequently used to study the pathophysiology of AF.

The first Chapter of the thesis describes how temporary pacing in horses can be performed. A pacing catheter, connected with an external electrical pulse generator, is introduced in the external jugular vein and advanced into the right atrium. Electrogram recordings and echocardiography are used to verify the position of the catheter tip. Once the electrodes of the catheter tip make contact with the atrial endocardium, cardiac pacing can be performed.

One must be aware that, in order to initiate a cardiac depolarisation in excitable myocardial tissue, i.e. in order to achieve capture, the electrical pulse must be of sufficient intensity to exceed the threshold for stimulation. The intensity of the electrical pulse is determined both by the pulse strength (amplitude) and by the duration (width) of the pulse. The strength-duration curve describes which combinations of pulse strength and duration are sufficient to reach the threshold for stimulation. In the study, three different approaches were used to determine the atrial strength-duration curve. With the fixed pulse width method, at a series of pulse widths, minimal amplitudes were determined to achieve capture. The strength-duration curve is obtained by connecting the different points. With the fixed amplitude method, the corresponding threshold pulse widths were determined at several fixed amplitudes. The third method proved to be the best one and was a combination of both aforementioned methods. At high amplitude the minimal pulse width was determined and at long pulse duration the minimal pulse strength was determined. From these two points the strength-duration curve was calculated using a mathematical equation.

Chapter 2 describes how the pacing technique was subsequently used to treat a horse with atrial flutter. This horse was a 5-year-old
Warmblood mare that was presented with loss of performance due to atrial fibrillation. Cardiac ultrasound indicated mild tricuspid valve insufficiency with right atrial enlargement. A standard treatment with quinidine sulphate changed the atrial rhythm from AF into atrial flutter but, because toxic effects occurred, the treatment had to be discontinued. After side effects had abolished, atrial flutter persisted and the horse was not able to return to work.

In man, termination of atrial flutter can be achieved by rapid atrial pacing. Seven months after the occurrence of atrial flutter, rapid atrial pacing was performed in the horse and sinus rhythm was successfully restored. Re-examination after a rest period indicated that sinus rhythm was still present and that tricuspid valve insufficiency and right atrial enlargement were less pronounced. The horse was brought back into training and returned to its previous level of athletic performance. At present, 5 years after the pacing procedure, sinus rhythm is still maintained and no complaints are reported.

The study proofs that atrial pacing provides an alternative treatment for atrial flutter in equines.

After research on temporary atrial pacing, the study was extended to perform permanent pacing. Chapter 3 illustrates the development of a feasible and safe technique to perform permanent pacing in 6 healthy equines by implantation of a pacemaker. Dual chamber pacemakers were used, which means that an atrial as well as a ventricular electrode were implanted, allowing stimulation of both cardiac chambers. A major advantage of the technique was that the whole implantation procedure could be performed in the standing, sedated animal, thereby avoiding a general anaesthesia. Atrial and ventricular leads were transvenously inserted through the cephalic vein and a subcutaneous pacemaker pocket was created between the lateral pectoral groove and the manubrium sterni. Positioning of each lead was guided by echocardiography and by measuring the electrical characteristics of the lead. The implantation procedure lasted about 4
hours in each animal and was well tolerated. In all animals dual chamber pacemaker function was obtained and results remained good throughout the follow-up period. At the time of implantation atrial and ventricular sensing were between 2.1 and 7.2 millivolt and 7.8 and 16.8 millivolt, respectively, and atrial and ventricular pacing thresholds at 0.5 millisecond varied from 0.5 to 0.7 volt and 0.3 to 1.0 volt, respectively. Six months after the implantation sensing values varied from 2 to 10 millivolt for the atrial lead and from 2 to 16 millivolt for the ventricular lead, while pacing thresholds at 0.5 millisecond varied from less than 0.5 to 2.5 volt for the right atrium and from less than 0.5 to 5.0 volt for the right ventricle. Atrial lead dislodgement occurred in 2 animals, requiring insertion of a new lead. Ventricular lead dislodgement was not observed.

The current research opens new prospects in the treatment of cardiac rhythm disturbances in equines.

Because now, implantation of a dual chamber pacemaker could be performed in a reproducible manner, the technique was put into practice by treatment of a horse with symptomatic bradycardia (Chapter 4). The horse was a 5-year-old gelding that presented syncope at termination of exercise. A 24-hour ECG recording revealed intermittent pauses in the sinus rhythm of up to 10 seconds, without any ventricular escape beat, indicating sinus node disease. Especially at termination of exercise, pauses in sinus rhythm were repeatedly present.

We assumed that implantation of a dual chamber pacemaker would prevent further syncope by preserving a minimal heart rate. However, this would be a fixed minimal rate and would not allow the horse to perform exercise. Therefore, a dual chamber pacing system with rate-adaptive function was implanted. Rate-adaptive pacing based on a built-in activity sensor, prevented excessive post-exercise bradycardia and syncope, allowing the horse to perform exercise. The location of the pacemaker at the level of the pectoral muscles proved
to be suitable resulting in appropriate sensor activation. At present, one year after initial admission, proper pacemaker function has allowed the horse to return back to its normal work.

This chapter illustrates that pacemaker implantation is a feasible therapy in horses and the use of a rate-adaptive pacing system further expands our treatment possibilities.

In the **second section** of the thesis, atrial pacing was applied to perform research on AF in horses. Lone AF, i.e. AF without underlying heart disease, is thought to be present in many AF horses and most of the time it is encountered in a subacute or chronic form. However, little information is available on the cause and effect of AF in horses. In the second section of the thesis, first a model for chronic AF is developed, trying to mimic the natural state of the disease as close as possible. Subsequently the AF model was applied to study AF pathophysiology in equines.

The first model for chronic AF, discussed in **Chapter 5**, consisted of the implantation of an electrical pulse generator, connected with a transvenous screw-in electrode that had been positioned in the right atrium of a healthy pony. The pulse generator was programmed to deliver every 4 seconds a burst of electrical stimuli to the right atrium to induce bouts of AF. Each burst consisted of a 2-second lasting train of electrical stimuli (20 Hz, 2 volt in amplitude and 0.5 millisecond pulse width). Initially, cessation of burst pacing resulted in short (less than 1 minute) self-terminating episodes of AF. As burst pacing continued, the duration of induced AF paroxysms became longer. After 3 weeks of atrial pacing, AF became sustained (56 hours). Although AF is hardly ever seen in healthy ponies, this model supports the concept that once AF starts it sets up changes in the electrical characteristics of the atrium that favour AF perpetuation.
This model of pacing-induced AF can be used to study the mechanisms of AF occurrence, its perpetuation and possible therapies.

In order to study the electrophysiologic aspects that contribute to AF pathophysiology, a new equine model for chronic AF was developed (Chapter 6). In 4 healthy ponies a dual chamber pacemaker, with an adapted pacemaker program, was implanted transvenously in the standing animal. The fibrillation program continuously analysed the intra-atrial and intraventricular electrogram. Below a ventricular rate of 80 beats per minute, an algorithm was activated that analysed atrioventricular synchrony. Sinus rhythm was defined as 1/1 atrioventricular synchrony during 3 to 4 consecutive heart cycles. Upon SR detection, a 2 second burst of stimuli (42 Hz) was delivered to the right atrium at double threshold in order to induce AF paroxysms. As a result of repeated pacing, the heart was kept continuously in AF. The advantage of this model is that simultaneous with a surface ECG, the intra-atrial electrogram can be recorded to determine the atrial electrogram morphology and rate of fibrillation. Programmed electrical stimulation can also be used to determine sinus node recovery time and atrial effective refractory period. By measuring atrial refractoriness at different pacing rates, rate adaptation of refractoriness can be assessed. The number of atrial depolarisations following the first captured extrastimulus during refractory period measurement estimates atrial vulnerability.

In conclusion, this model is suited to study AF in equines because it reflects closely the natural appearance of the disease and because it provides an excellent means to analyse electrophysiologic alterations that might be induced by AF.

The latter model was applied to study the effect of experimentally induced AF on healthy equines (Chapter 7). Four ponies, with the above-mentioned fibrillation pacemaker implanted, were used in this study. With the pulse generator, atrial fibrillation was maintained during
6 months by applying intermittent burst pacing. Electrophysiologic measurements, determination of intracardiac blood pressure and echocardiography were performed at baseline, at several time points during the 6 months of fibrillation and after the fibrillation period. In the present study, additional left atrial measurements were introduced to estimate atrial contractility. To avoid confounding effects of irregular heart rate and to obtain reproducible results for pressure and cardiac ultrasound, heart catheterisations and cardiac ultrasound were performed during sinus rhythm when the atrium was paced at a fixed rate. During the fibrillation period, this could be achieved by temporarily disabling the fibrillation program in order to allow sinus rhythm to restore spontaneously.

As a result of maintained AF, atrial refractoriness decreased and the adaptation to rate was attenuated. Fibrillation rate increased and the atrial electrogram morphology became more complex. No change in sinus node function was demonstrated. A slight increase in right atrial pressure was observed and a significant left atrial dilatation became apparent. Non-invasive assessment of atrial shortening fraction indicated a total loss of atrial contractile function as a result of fibrillation. These findings were confirmed by blood pressure values: pressure change and rate of pressure rise during atrial contraction were both significantly decreased. Because of atrial contractile dysfunction, ventricular filling was decreased. Consequently, a depressed ventricular function by the Frank-Starling mechanism resulted in a decreased stroke volume.

During the fibrillation period, the duration of the induced atrial fibrillation paroxysms increased progressively and became persistent in one animal, requiring defibrillation. Duration of the fibrillation episodes was associated with atrial diameter, atrial refractory period and rate of fibrillation.

After restoration of SR, the electrophysiological variables returned to normal within 10 days. Atrial size and atrial contractile function only
normalized after 1 to 2 months of SR. The duration of the induced AF paroxysms abruptly decreased to less than a minute. All fibrillation-induced alterations were reversible within 2 months after cardioversion.

The final conclusion of the thesis is that atrial pacing can be successfully applied in equines and that the pacing procedure is well tolerated, even without application of sedatives. Temporary as well as permanent pacing techniques open new perspectives on the diagnosis and treatment of equine rhythm disorders. The chronic AF model provided essential information on AF pathophysiology and can be used for future research developing new therapeutic strategies.
SAMENVATTING

In de humane cardiologie is elektrische stimulatie van het hart, meestal kortweg ‘pacing’ genoemd, een onmisbare techniek geworden voor de diagnosestelling en de behandeling van verschillende aritmieën. Om de pathofysiologie van hartritmestoornissen bij de mens beter te bestuderen wordt het pacen vaak toegepast in experimentele diermodellen. Paarden worden echter slechts zelden gebruikt voor dergelijke modellen en omdat bij het paard ook nauwelijks diepgaand onderzoek wordt verricht op gebied van hartritmestoornissen zijn zowel de diagnostische als de therapeutische mogelijkheden bij deze diersoort sterk gelimiteerd.

Bij het paard is atriale fibrillatie (AF) klinisch de belangrijkste hartaritmie, maar zelfs van deze aandoening is de onderliggende pathofysiologie nog grotendeels onbekend. Deze doctoraatsthesis heeft dan ook als doel om door middel van het ontwikkelen van een techniek om het paardenhart te pacen, de pathofysiologie van hartritmestoornissen op te helderen en zo nieuwe perspectieven te openen voor de behandeling ervan.

De algemene aspecten van atriale pacing en van atriale fibrillatie worden uiteengezet in de introductie van dit proefschrift.

In het eerste gedeelte ervan wordt een overzicht gegeven van de prikkelbaarheid van het hart en van het materiaal dat nodig is om een hart elektrisch te kunnen stimuleren. Het gebruik van elektrische hartstimulatie in de humane geneeskunde wordt aangehaald waarbij vooral nadruk wordt gelegd op de diagnostische en de therapeutische toepassingen. Vervolgens worden de beschikbare literatuurgegevens over elektrische hartstimulatie bij paarden weergegeven. Er wordt hierbij zowel ingegaan op pacen met therapeutische doeleinden als op pacen toegepast tijdens cardiale studies.
Samenvatting

Het tweede deel van de introductie bespreekt de elektrofysiologische aspecten van atriumfibrillatie in het algemeen en gaat vervolgens dieper in op atriale fibrillatie bij het paard in het bijzonder. Klinische gegevens wijzen erop dat AF aanleiding geeft tot verminderde prestaties. Het juiste verband echter tussen AF en pathologische veranderingen aan het hart, zoals bijvoorbeeld atriale dilatatie, verminderde atriale contractiliteit, ventriculaire disfunctie, histologische en elektrofysiologische veranderingen, blijft nog altijd onopgehelderd.

Het onderzoek van deze doctoraatsthesis bestaat uit twee grote onderdelen. De eerste sectie (Hoofdstukken 1-4) beschrijft de totstandkoming van een techniek om het paardenhart elektrisch te stimuleren. Zowel tijdelijke als permanente stimulatie komen hierbij aan bod en beiden worden gebruikt ter behandeling van klinische patiënten. In de tweede sectie van de thesis (Hoofdstukken 5-7) worden de pacingtechnieken aangewend om een experimenteel paardenmodel voor chronische atriale fibrillatie te ontwikkelen. Dit model wordt ten slotte gebruikt om de pathofysiologische aspecten van AF bij het paard te bestuderen.

Het eerste Hoofdstuk van de thesis beschrijft de ontwikkeling van een techniek om temporaire pacing bij paarden uit te voeren door middel van een pacing-katheter. Ter hoogte van de top van de katheter zitten twee elektrodes ingebouwd. Het andere uiteinde van de katheter is voorzien van connecties die verbonden worden met een elektrische pulsgenerator. De top van de katheter wordt in de vena jugularis externa ingebracht en vervolgens intraveneus opgeschoven naar het rechter atrium tot de elektrodes contact maken met het atriale endocard. De juiste positie van de kathetertop wordt gecontroleerd door middel van echocardiografie en een intracardiaal elektrogram. Een belangrijke voorwaarde om een hart elektrisch te kunnen stimuleren, dus om een depolarisatie van myocardiaal weefsel te
kunnen veroorzaken, is het toedienen van een elektrische prikkel die sterk genoeg is om de drempel voor stimulatie te overschrijden. De intensiteit van een elektrische prikkel wordt bepaald door zowel de amplitude (strength) als de duur (duration) van de prikkel. In Hoofdstuk 1 worden drie verschillende manieren beschreven om een strength-duration curve op te stellen. Dit is een curve die beschrijft welke combinaties van amplitude en duur geschikt zijn om de stimulatiedrempel te bereiken. Bij de vaste-prikkelduur-methode worden minimale amplitudes bepaald die nodig zijn om bij een welbepaalde prikkelduur de drempel te bereiken. Bij de vaste-prikkelamplitude-methode wordt vastgesteld welke minimale prikkelduur nodig is om bij een welbepaalde prikkelamplitude de stimulatiedrempel te bereiken. Bij een derde methode worden twee punten op de strength-duration curve bepaald met behulp van beide voorgaande methodes: voor een hoge amplitude wordt de overeenkomstige pulsduur bepaald en voor een lange pulsduur wordt de amplitude bepaald om de drempelwaarde voor stimulatie te bereiken. Aan de hand van deze 2 punten wordt de rest van de curve berekend op basis van een formule.

Het wordt duidelijk dat temporaire atriale pacing wel degelijk kan toegepast worden bij het paard mits de prikkelintensiteit de drempelwaarde voor stimulatie overschrijdt.

Hoofdstuk 2 beschrijft hoe de temporaire pacing techniek kan gebruikt worden om een paard met atriale flutter te behandelen. Een 5-jarige warmbloed merrie werd aangeboden wegens vermindere prestaties ten gevolge van boezemfibrilleren. Echocardiografie toonde een milde insufficiëntie aan van de tricuspidaklep met vergroting van het rechter atrium. De standaardbehandeling met quinidinesulfaat veranderde het hartritme van atriale fibrillatie in atriale flutter, maar aangezien toxische neveneffecten optraden, moest de therapie gestaakt worden.
SAMENVATTING

In de humane geneeskunde kan atriale flutter stopgezet worden door middel van snelle atriale pacing. Omdat een medicamenteuze therapie uitgesloten was, werd bij de warmbloedmerrie eveneens de snelle atriale pacing techniek toegepast. Zeven maand na het ontstaan van de atriale flutter werd met behulp van snel atriaal pacen het normaal sinusritme weer hersteld. Na een rustperiode toonde grondig hartonderzoek aan dat sinusritme nog steeds aanwezig was en dat zowel de tricuspidaalinsufficiëntie als de rechter atriumdilatatie minder uitgesproken waren. Daarop werd het paard weer in training gebracht waarbij het opnieuw zijn vorig prestatieniveau bereikte. Nu, vijf jaar na de pacing procedure, slaat het hart nog steeds in sinusritme en zijn er verder geen klachten.

Deze casuïstiek bewijst dat atriale pacing gebruikt kan worden als alternatieve behandelmethode voor atriale flutter.

In een volgende fase van de studie werd getracht om naast temporaire pacing eveneens een permanente pacing techniek voor het paard op punt te stellen. Hoofdstuk 3 illustreert de ontwikkeling van een reproduceerbare en tevens veilige techniek om door middel van pacemakerimplantatie het hart permanent elektrisch te stimuleren.

In deze studie werd bij zes gezonde dieren een tweekamer pacemaker geïmplanteerd, wat betekent dat zowel een atriale als een ventriculaire elektrode worden ingeplant zodat zowel het atrium als het ventrikel apart gestimuleerd kunnen worden. De implantatie werd uitgevoerd op gesedeerde doch rechtstaande dieren, waardoor een algemene anesthesie kon vermeden worden. Zowel de atriale als de ventriculaire lead werden ingeplant via de vena cephalica en de pacemaker zelf werd subcutaan ingebracht tussen het manubrium sterni en de zijdelingse borstgroeve. Beide leads werden in het hart gepositioneerd met behulp van echocardiografie en met behulp van metingen van sensing- en pacingvoltage en leadweerstand. De implantatieprocedure duurde gemiddeld vier uur en werd goed verdragen door alle dieren. Bij allen werd een tweekamer pacemaker
functie verkregen en de meetresultaten waren bevredigend gedurende de ganse follow-up periode. Op het tijdstip van implantatie waren de atriale en de ventriculaire sensing waarden respectievelijk 2,1 tot 7,2 millivolt en 7,8 tot 16,8 millivolt. De atriale en de ventriculaire drempelwaarden voor stimulatie bij 0,5 milliseconden varieerden van 0,5 tot 0,7 volt en van 0,3 tot 1 volt, respectievelijk. Zes maanden na de implantatie varieerden de sensingwaarden van de atriale lead van 2 tot 10 millivolt en van de ventriculaire lead van 2 tot 16 millivolt. Pacing drempelwaarden bij 0,5 milliseconden varieerden dan van minder dan 0,5 tot 2,5 volt voor het rechter atrium en van minder dan 0,5 tot 5 volt voor het rechter ventrikel.

Bij twee dieren kwam de atriale lead terug los en werd een nieuwe lead ingebracht. Loslating van een ventriculaire lead werd bij geen enkel dier geobserveerd.

In Hoofdstuk 4 werd de hierboven beschreven techniek voor een permanente pacemakerimplantatie aangewend als therapie bij een paard met symptomatische bradycardie. Een 5-jarige ruin werd immers aangeboden op de kliniek met de klacht van syncope na inspanning. Een 24-uur ECG toonde intermitterende pauzes in het sinusritme aan die tot 10 seconden duurden zonder dat er enig ventriculair escaperitme optrad, gegevens die wijzen op een aandoening van de sinusknoop. Vooral vlak na inspanning waren er herhaaldelijk pauzes in het sinusritme te zien.

Implantatie van een tweekamer pacemaker zou verdere syncopes kunnen vermijden door steeds een minimaal hartritme te garanderen. Zo'n constant maar laag hartritme zou echter geen fysieke inspanningen toelaten. Daarom werd hier geopteerd voor een tweekamer pacemaker met een ritmerespons. Pacing met ritmerespons, steunend op een ingebouwde activiteitssensor, verhinderde succesvol bradycardie en syncopes na inspanning, en maakte het mogelijk om het paard terug op een normale manier in training te brengen. De lokalisatie van de pacemaker ter hoogte van
de voorste oppervlakkige borstspier bleek geschikt te zijn om een gepaste sensor activatie te verkrijgen. Momenteel, 1 jaar na de implantatie, zorgt het goed functioneren van de pacemaker ervoor dat het paard nog steeds zonder problemen bereden kan worden.

Pacemaker implantatie is dus een haalbare therapie bij het paard en door de toepasbaarheid van de ritmerespons functie kan de pacemaker functie nog beter afgestemd worden aan de behoefte van het individu waardoor zelfs fysieke inspanning opnieuw mogelijk wordt.

In de tweede sectie van dit doctoraatswerk werd atriale pacing niet therapeutisch maar experimenteel aangewend om verder onderzoek uit te voeren met betrekking tot atriale fibrillatie bij het paard.

Bij de meeste paarden met ‘natuurlijke’ AF wordt de aandoening in het subacuut of chronisch stadium vastgesteld en vaak kan er geen onderliggende hartafwijking aangetoond worden. Tot op heden is er slechts weinig informatie voorhanden over de oorzaak van AF bij het paard en de gevolgen ervan op de hartspier op langere termijn.

In het tweede deel van de huidige studie was het daarom de bedoeling eerst een experimenteel model te ontwikkelen om chronische AF bij het paard te induceren en daarbij het natuurlijke ziekteproces zo getrouw mogelijk na te bootsen. Vervolgens werd dit model dan gebruikt om de pathofysiologische gevolgen van AF op het paardenhart te bestuderen.

Het eerst ontwikkelde model voor chronische atriale fibrillatie (Hoofdstuk 5) werd toegepast bij een gezonde pony en bestond uit een ingeplante elektrische pulsgenerator, verbonden met een transvenueuze schroefelektrode ter hoogte van het rechter atrium. De pulsgenerator was geprogrammeerd om elke vier seconden een trein (burst) van elektrische stimuli (20 Hz, 2 volt en 0,5 milliseconden) in het rechter atrium te genereren met de bedoeling een AF episode te induceren. Initieel resulteerde een stopzetting van burst pacing in korte
SAMENVATTING

(<1 minuut) zelfuitdovende episodes van AF. Hoe langer burst pacing echter werd toegepast hoe langer het geïnduceerde AF paroxisme bleef bestaan. Na drie weken van atriaal pacen bleek de geïnduceerde fibrillatie episode gedurende een periode van 56 uur op zichzelf verder bestaan. Hoewel AF zelden voorkomt bij gezonde pony’s doen deze bevindingen vermoeden dat AF, eens aanwezig in een hart, zodanige veranderingen teweegbrengt in de elektrische eigenschappen van het atrium, dat AF als het ware zichzelf in stand houdt.

Om het onderzoek toe te spitsen op de elektrofysiologische aspecten die bijdragen tot de pathofysiologie van fibrillatie werd een nieuw model voor chronische AF ontwikkeld (Hoofdstuk 6).

Bij 4 gezonde pony’s werd een tweekamer pacemaker, die van aangepaste software voorzien was, ingeplant. Deze software analyseerde voortdurend het intra-atriaal en intraventriculair elektrogram. Wanneer het ventriculair ritme van de pony’s lager lag dan 80 slagen/min werd een algoritme geactiveerd dat de atrioventriculaire doorgeleiding analyseerde. Sinusritme werd gedefinieerd als 1/1 atrioventriculaire doorgeleiding gedurende 3 à 4 opeenvolgende hartcycli. Bij detectie van sinusritme werd een twee seconden durende burst van elektrische stimuli (42 Hz) gegenereerd ter hoogte van het rechter atrium met een intensiteit van twee maal de drempelwaarde voor stimulatie, en dit om telkens een AF paroxisme te induceren. Door dit herhaald pacen werd het hart dus continu in AF gehouden.

Het grote voordeel van dit model is dat, tegelijkertijd met een oppervlakte ECG, een intra-atriaal elektrogram kan opgenomen worden ter bepaling van de morfologie van dit atriaal elektrogram en van de snelheid van fibrilleren. Het toedienen van geprogrammeerde stimuli kan eveneens gebruikt worden om de sinusknoop activiteit (recovery-time) evenals de atriale effectieve refractaire periode te bepalen. Door het meten van de atriale refractaire periode bij
verschillende pacing frequenties kan ook de aanpassing van de refractaire periode aan het atriale ritme bepaald worden. Het meten van het aantal atriale depolarisaties volgend op de eerste ‘gevolgde’ extrastimulus tijdens de refractaire periode kan gebruikt worden om de atriale gevoeligheid in te schatten.

Omdat al deze metingen gemakkelijk uitvoerbaar zijn, mag men concluderen dat dit chronisch AF-model de ideale middelen verschaf voor de studie van elektrofysiologische veranderingen die mogelijks een ‘natuurlijke’ AF induceren of in stand houden.

Het model werd daarom gebruikt om bij gezonde paarden het effect van experimenteel geïncurveerde AF na te gaan (Hoofdstuk 7). Bij de vier gezonde pony’s die voor deze proefopzet werden gebruikt, werd, met bovengenoemde pacemaker implantatie, AF gedurende zes maand in stand gehouden met behulp van intermitterende burst pacing. Elektrofysiologische metingen, intracardiale bloeddrukmetingen en echocardiografie werden uitgevoerd voor, tijdens en na de fibrillatieperiode. Bij deze proefopzet werden tevens nieuwe metingen geïntroduceerd om gedurende elke hartcyclus de atriale contractiliteit te kunnen beoordelen. Om storende effecten van een onregelmatig hartritme hierbij te vermijden en om reproduceerbare resultaten qua bloeddruk en echocardiografie te bekomen, werden de hartkatheterisaties uitgevoerd bij een sinusritme terwijl het atrium gestimuleerd werd aan een vooraf vastgelegde snelheid. Gedurende de fibrillatieperiode kon dit gebeuren door het fibrillatieprogramma tijdelijk uit te schakelen en te wachten tot sinusritme spontaan heroptrad.

Op basis van de meetresultaten werd vastgesteld dat tengevolge van de langdurige AF de atriale refractaire periode verkort was en de frequentierespons verminderd. De fibrillatiesnelheid verhoogde en de morfologie van het atriale elektrogram werd steeds complexer. In de sinusknoopfunctie zelf konden geen veranderingen aangetoond worden. Een lichte stijging van de rechter atriale bloeddruk werd
waargenomen evenals een significantie dilatatie van het linker atrium. De niet-invasieve bepaling van de atriale verkortingsfractie duidde op een totaal verlies van atriale contractiliteit ten gevolge van de fibrillatie. Deze bevindingen werden tevens bevestigd door de gemeten bloeddrukwaarden: de gegenereerde druk en de snelheid van de bloeddrukstijging gedurende een atriale contractie waren beiden significant gedaald. Ten gevolge van de atriale contractiele disfunctie was de ventriculaire vulling eveneens gedaald. De daardoor verminderde ventriculaire functie (Frank-Starling mechanisme) resulteerde in een verminderd slagvolume. Gedurende de fibrillatieperiode nam de duur van de geï nduceerde AF progressief toe en werd bij 1 dier zelfs blijvend. In dit laatste geval moest defibrillatie uitgevoerd worden om het sinusritme te herstellen. De duur van de fibrillatie-episodes was gecorreleerd met de atriale diameter, de atriale refractaire periode en de fibrillatiesnelheid. Na herstel van het sinusritme keerden de elektrofysiologische variabelen terug naar de normaalwaarden binnen een periode van 10 dagen. Ook de duur van het geï nduceerde AF paroxisme daalde abrupt tot minder dan 1 minuut. Atriale diameter en atriale contractiliteit normaliseerden pas na 1 à 2 maand.

Uit de studie is dus gebleken dat AF verscheidene veranderingen teweegbrengt ter hoogte van het hart maar dat ze volledig reversibel blijken te zijn en dit binnen de twee maand na cardioversie.

De globale conclusie van dit doctoraal proefschrift is dat atriale pacing wel degelijk kan uitgevoerd worden bij paarden en dat de gehele pacing procedure, zelfs zonder gebruik van sedativa, goed verdragen wordt. Zowel tijdelijke als permanente pacing technieken openen nieuwe perspectieven wat betreft diagnosestelling en behandelmogelijkheden voor hartritmestoornissen bij het paard.
Het chronisch AF model verschaft essentiële informatie over de pathofysiologie van AF en kan zeker gebruikt worden bij de ontwikkeling van nieuwe therapeutische strategieën.
Hoewel alleen mijn naam op het titelblad van dit proefschrift verschijnt zou dit eigenlijk een lange lijst moeten zijn van alle personen die geholpen hebben bij het realiseren van dit werk. Ongetwijfeld worden sommige mensen niet vermeld hoewel ik ze toch wens te danken.

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doctoraatsopleiding in de diergeneeskundige wetenschappen waarvan op 10 september 1999 het getuigschrift behaald werd.

Gunther van Loon is auteur of mede-auteur van 26 publicaties in internationale en nationale tijdschriften en was 4 maal spreker op een internationaal congres.


lipoid pneumonia in a horse. *Equine Vet J*, accepted for publication.


**ORAL PRESENTATIONS AND POSTERS**


of the 5th World Equine Veterinary Association, September 10th – September 12th 1997, Padova, Italy, p 75.


