Pacing induced sustained atrial fibrillation in a pony

Gunther van Loon, René Tavernier, Mattias Duytschaever, Winoc Fonteyne, Piet Deprez, Luc Jordaens

Abstract

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 favor its own perpetuation.

Résumé

Une électrode transveineuse vissable fut implantée dans l'oreillette droite d'un poney en santé et branché à un générateur de pulsations programmé pour envoyer des influx de stimuli électrique à l'oreillette. Initialement, l'arrêt des influx rythmiques a entraîné de courts épisodes (moins de 1 minute) auto-limitants de fibrillation auriculaire. Avec la poursuite des influx rythmiques, les épisodes de fibrillation auriculaire induits s'allongeaient. Après 3 semaines de stimulation continue, la fibrillation auriculaire devint soutenue (56 heures). Le modèle de fibrillation auriculaire rythmique induite décrit pourrait être utilisé pour étudier les mécanismes entraînant la fibrillation auriculaire, son maintien et sa thérapie. Les observations préliminaires supportent le concept qu'une fois que la fibrillation auriculaire apparaît, elle induit des changements dans les caractéristiques électriques de l'oreillette et favorise ainsi son maintien.

(Traduit par docteur Serge Messier)

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). Atrial fibrillation produces adverse hemodynamic effects because atrial contraction is absent and no longer contributes to optimal ventricular filling. During AF, 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 that have a large heart (eg, horses) and occurs less in animals that have 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.

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, Minnesota, USA). 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 by administering trimethoprim-sulfadiazin (Borgal; Hoechst Roussel Vet, Brussels, Belgium), 15 mg/kg, IV. During the whole implantation procedure, the pony remained in standing position and was given detomidine (Domosedan; Pfizer Animal Health, Nossegem, Belgium), 20 mg/kg, IV, and buprenorphine (Temgesic; Schering-Plough, Brussels, Belgium), 2 μg/kg IV. A base-apex ECG (Cardiolife TEC-7511K; Nihon Kohden, Tokyo, Japan) was connected and cardiac ultrasonography was performed from the right hemithorax. The

Department of Large Animal Internal Medicine, Faculty of Veterinary Medicine, University of Ghent, Salisburylaan 133, B-9820 Merelbeke, Belgium (van Loon, Deprez); Department of Cardiology, University Hospital, University of Ghent, De Pintelaan 185, B-9000 Ghent, Belgium (Tavernier, Duytschaever, Fonteyne, Jordaens).

Address correspondence and reprint requests to Dr. Gunther van Loon, telephone: +32 9 264 7584, fax: +32 9 264 7796, e-mail: Gunther.vanLoon@rug.ac.be.

Received February 16, 2000. Accepted July 18, 2000.

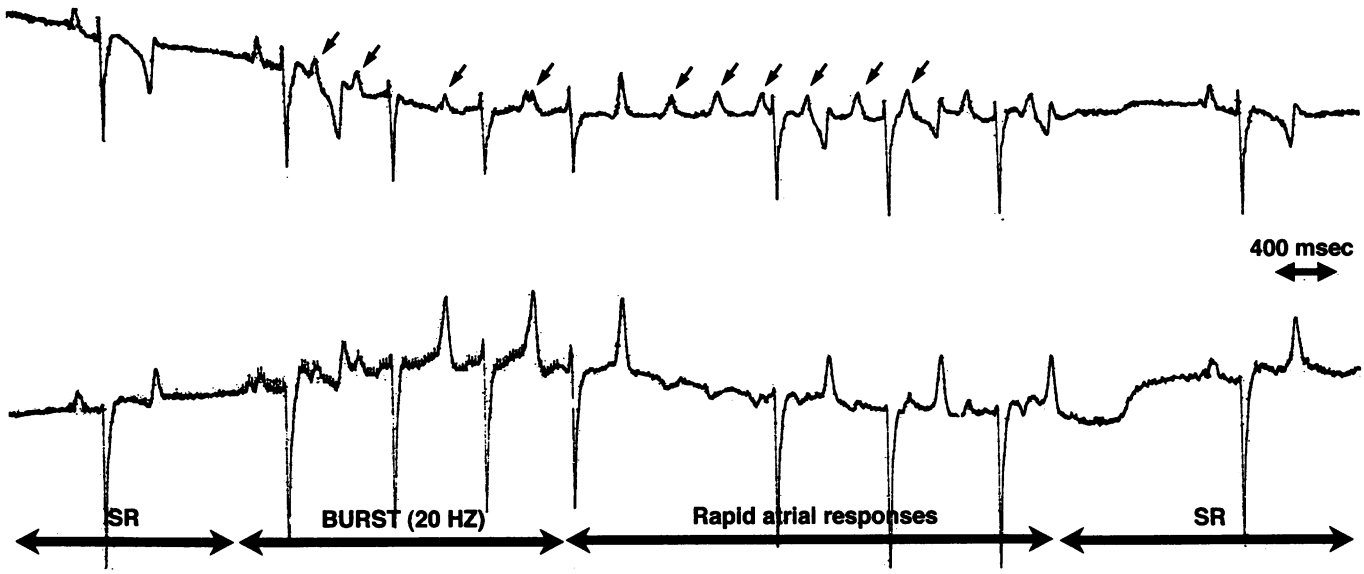

Figure 1. Surface ECG (unipolar lead on the upper trace and lead II on the lower trace) on Day 0. During the burst, small spikes, resulting from the pacing stimulus artifact, and rapid atrial responses are present. The electrically induced atrial depolarizations, P'-waves (arrows), are separated by isoelectric segments. After cessation of the burst, atrial responses continue during 3 s before restoration of sinus rhythm (SR).

region of the left lateral pectoral groove was surgically prepared and injected with local anesthetic. 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) was introduced in the vein and advanced towards the heart. When entrance of the lead tip in the right atrium was visualized 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 analyzer (Pacing System Analyzer Model 5309, Medtronic). With the pacing system analyzer, electrical pulses of variable intensity could be generated and lead impedance and intrinsic cardiac activity could be measured. Subsequently, the lead was slowly maneuvered 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 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 4/1; Johnson & Johnson). 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 wk.

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

Measurements were made on the day pacing was started (Day 0), after 1 and 3 d and after 1, 2, and 3 wk. 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. Sustained AF was defined as AF of more than 24 h (7). 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 of the University of Ghent.

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.

During the experiment, the configuration of the atrial responses changed. This was best visualized on the unipolar ECG. On Day 0, a rapid repetition of electrically induced atrial depolarizations (P'-waves) separated by isoelectric segments was seen during and sometimes after the burst, indicating that rapid atrial responses with an organized atrial activation were present, rather than AF (Figure 1). On Day 0, only in 12 out of 20 bursts, rapid atrial responses were present after cessation of the burst.

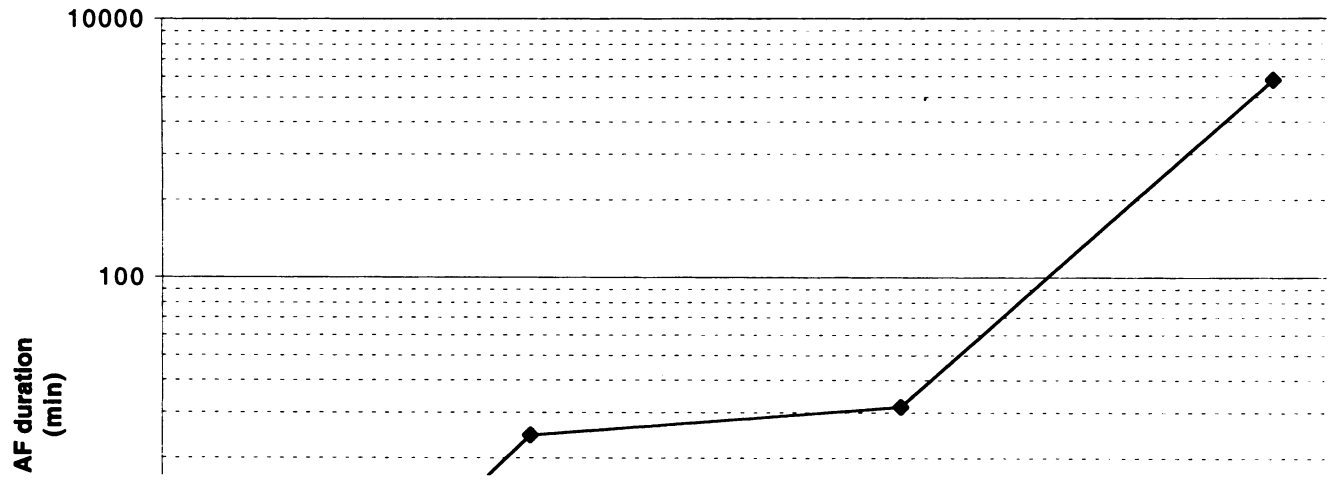

Figure 2. Surface ECG (unipolar lead on the upper trace and lead II on the lower trace) after 1 d of burst pacing. The pulse generator is just turned off. AF is present.

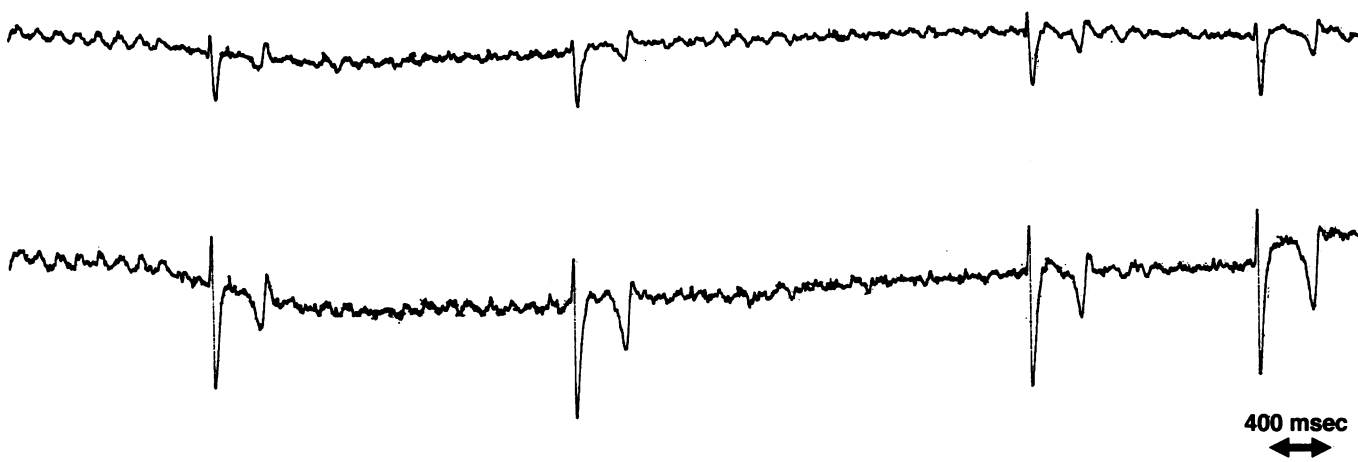

Figure 3. Duration of AF in the ordinate (logarithmic scale) versus the time atrial burst pacing is applied. The longer burst pacing is continued, the longer the induced AF episodes. On Day 21 sustained AF is present.

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 (Figure 2). From this day onwards, every burst was followed by an episode of AF.

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 s, with a range of 0.5 to 3 s. After 1 d of pacing, the induced AF episodes were short, with a mean of 2 s, ranging from 0.5 to 10 s (over 5 inductions) (Figure 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 s (range 2 to 20 s). After 1 and 2 wk of pacing respectively,

the mean AF duration had further increased to 6 min (range 4 to 8 min over 3 attempts) and 10 min (range 4 to 15 min over 3 attempts). After 3 wk of burst pacing, there was no restoration of SR after inactivation of the stimulator and sustained AF (AF lasting for more than 24 h) was present. The pulse generator was left inactive and daily ECG examinations indicated that fibrillation continued. Finally, after 56 h of AF, SR restored spontaneously.

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. The vulnerability of the atria to fibrillation increased and the duration of the induced AF episodes prolonged progressively. Three weeks of burst pacing resulted in sustained AF (> 24 h duration).

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 is present, the probability that they will die out altogether is high, and the arrhythmia is likely to terminate itself. The higher the number of wavelets, the smaller the chance they will 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 AF episodes induced initially 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 (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 remodelling. The decreased atrial refractory period shortens the wavelength of the atrial impulse and allows more fibrillation waves to coexist in the atria. Atrial fibrillation, therefore, seems to lead to its own progression. Besides a shortening in refractory period, burst pacing in dogs 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 the configuration of the atrial response and an increase in the rate of fibrillation has 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.

Atrial fibrillation 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 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 anesthesia, this problem can be overcome. During our study, burst pacing was only performed over 3 wk, 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 extra-stimuli. This will allow for study of the electrical characteristics of the atrium in more detail. Furthermore, this approach would lead to the development of reliable methods of inducing AF. This, in turn, will allow for evaluation of the effects of different interventions on the inducibility and, therefore, the prevention, of AF. These interventions include the administration of drugs as well as the use of pacing algorithms to prevent AF.

Acknowledgments

The authors wish to thank the Special Research Fund, University of Ghent, for their financial support.

References

1. Fogoros RN. Electrophysiologic testing. Oxford: Blackwell Science, 1995.
2. Moore EN, Spear JF. Electrophysiological studies on atrial fibrillation. Heart Vessels 1987;Suppl 2:32–39.
3. De Luna AB, Genis AB, Guindo J, et al. Méchanismes favorisant et déclenchant la fibrillation auriculaire. Arch Mal Coeur 1994; 87:19–25.
4. Benditt DG, Dunbar D, Fetter J, Sakaguchi S, Lurie KG, Adler SW. Low-energy transvenous cardioversion defibrillation of atrial tachyarrhythmias in the canine: An assessment of electrode configurations and monophasic pulse sequencing. Am Heart J 1994;127:994–1002.
5. Morillo CA, Klein GJ, Jones DL, Guiraudon CM. Chronic rapid atrial pacing. Structural, functional and electrophysiological characteristics of a new model of sustained atrial fibrillation. Circulation 1995; 91:1588–1595.
6. Sokoloski MC, Ayers GM, Kumagai K, Khrestian CM, Niwano S, Waldo AL. Safety of transvenous atrial defibrillation: studies in the canine sterile pericarditis model. Circulation 1997;96:1343–1350.
7. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 1995;92:1954–1968.

8. Holmes DR, Hayes DL. Pacemaker implantation techniques. In: Saksena S, Goldschlaber N, eds. Electrical therapy of cardiac arrhythmia. Philadelphia: WB Saunders, 1990:173–190.
9. Brinker J, Midei M. Techniques of pacemaker implantation. In: Ellenbogen KA, ed. Cardiac pacing. Abingdon: Blackwell Science, 1996:216–277.
10. Moe GK. On the multiple wavelet hypothesis of atrial fibrillation. Arch Int Pharmacodyn 1962;140:183–188.
11. Elvan A, Wylie K, Zipes DP. Pacing-induced chronic atrial fibrillation impairs sinus node function in dogs: Electrophysiological remodeling. Circulation 1996;94:2953–2960.
12. Blissitt KJ. Diagnosis and treatment of atrial fibrillation. Equine Vet Educ 1999;11:11–19.
13. Brignole M, Menozzi C, Sartore B, Barra M, Monducci I. The use of atrial pacing to induce atrial fibrillation and flutter. Int J Cardiol 1986;12:45–54.
14. Cooper RA, Alferness CA, Smith WM, Ideker RE. Internal cardioversion of atrial fibrillation in sheep. Circulation 1993;87: 1673–1686.
15. Sideris DA, Toumanidis ST, Tselepatiotis E, et al. Atrial pressure and experimental atrial fibrillation. Pacing Clin Electrophysiol 1995;18:1679–1685.
16. Power JM, Beacom GA, Alferness CA, et al. Susceptibility to atrial fibrillation: a study in an ovine model of pacing-induced early heart failure. J Cardiovasc Electrophysiol 1998;9:423–435.
17. Osswald S, Trouton TG, Roelke M, et al. Transvenous single lead atrial defibrillation: efficacy and risk of ventricular fibrillation in an ischemic canine model. Pacing Clin Electrophysiol 1998; 21:580–589.
18. Senta T, Kubo K. Experimental induction of atrial fibrillation by electrical stimulation in the horse. Exp Rep Equine Health Lab 1978;15:37–46.