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ScienceDirect

Journal of Electrocardiology 49 (2016) 124 – 131

JOURNAL OF Electrocardiology

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# A porcine model of early atrial fibrillation using a custom-built, radio transmission-controlled pacemaker☆

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**Abstract** Mechanisms underlying atrial remodeling toward atrial fibrillation (AF) are incompletely understood. We induced AF in 16 pigs by 6 weeks of rapid atrial pacing (RAP, 600 bpm) using a custom-built, telemetrically controlled pacemaker. AF evolution was monitored three times per week telemetrically in unstressed, conscious animals. We established a dose–response relationship between RAP duration and occurrence of sustained AF >60 minutes. Left atrial (LA) dilatation was present already at 2 weeks of RAP. There was no evidence of left ventricular heart failure after 6 weeks of RAP. As a proof-of-principle, arterial hypertension was induced in 5/16 animals by implanting desoxycorticosterone acetate (DOCA, an aldosterone-analog) subcutaneously to accelerate atrial remodeling. RAP + DOCA resulted in increased AF stability with earlier onset of sustained AF and accelerated anatomical atrial remodeling with more pronounced LA dilatation. This novel porcine model can serve to characterize effects of maladaptive stimuli or protective interventions specifically during early AF.


*Keywords:* Atrial fibrillation; Atrial remodeling; Rapid atrial pacing; Porcine; DOCA; Arterial hypertension

## Introduction

Atrial fibrillation (AF) is the most common chronic arrhythmia in developed countries with a prevalence rate of 1.5–2% in the general population [1,2]. AF increases the risk for stroke and heart failure and correlates with increased mortality [2]. It is associated with a number of risk factors including age, congestive heart failure, valvular disease, diabetes and hypertension [3]. Many of these risk factors cause elevated atrial pressures with subsequent chronic atrial stretch, which in turn promotes atrial arrhythmia [4].

Experimental and clinical data indicate that AF is a progressive disease [5–7]. The presence of AF induces electrical and structural atrial remodeling processes, which further manifest AF ("AF begets AF") [6]. In line with this concept, rhythm-control therapies in symptomatic AF-patients, i.e., the use of antiarrhythmic drugs and/or catheter ablation, are most successful in early stages of the disease [7]. However, in contrast to left ventricular failure, no therapy beyond risk factor control or catheter ablation has been established that attenuates atrial remodeling toward AF [8]. It thus appears reasonable to investigate pathophysiological changes and their response to risk factors and protective agents during early stages of atrial remodeling.

In this study, we present a large animal model of AF that was specifically designed to investigate early stages of atrial remodeling during the evolution of AF. A custom-designed pacemaker allowed for monitoring atrial rhythm in conscious animals within a distance of 5 meters telemetrically, such that onset and stability of AF could be identified reliably. As a proof of principle, we induced arterial hypertension experimentally and observed the effect of this risk factor on AF stability and early structural atrial remodeling.

☆ Conflict of interest: All authors declare that they have no conflict of interest.

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http://dx.doi.org/10.1016/j.jelectrocard.2015.12.012
0022-0736/

## Methods

The experimental protocol was approved by the local bioethics committee of Vienna, Austria (BMWF-66.010/0108-II/3b/2010), and conforms with the Guide for the Care and Use of Laboratory Animals published by the US National Institute of Health (NIH publication no. 85-23, revised 1996).

### *Custom-built pacemaker*

We designed and constructed a custom-built pacemaker device. This device consisted of a printed circuit board that was equipped with a ultra-low-power microcontroller (MSP430FR5739, Texas Instruments, Dallas, TX, USA), a 2.4 GHz radiofrequency transceiver (CC2591, Texas Instruments), two 3.6 V lithium thionyl chloride batteries (TLH-5934, Tadiran U.S. Battery Division, Lake Success, NY, USA), an IS1 socket (Osypka, Rheinfelden, Germany) that was compatible to commercial pacemaker probes, and a number of standard electronic components (semiconductors, resistors, capacitors, …). The device was embedded into biocompatible material (EPO-TEK® 301, Epoxy Technology, Inc., Billerica, MA, USA). A flexible IS1 extension was connected to the IS1 socket on the main board and remaining cracks were filled with biocompatible material. The device's final size was 72 × 48 × 12 mm and final weight was approximately 75 g (see Fig. 1A). The device underwent gas sterilization before implantation.

The custom-built pacemaker device was capable to generate rectangular impulses with a fixed amplitude of 3.2 V and a variable, programmable duration (0.1–10 ms in steps of 0.1 ms). There were three major advantages compared to commercially available pacemaker devices. First, there was virtually no upper limit for the stimulation frequency, which allowed for rapid atrial pacing at 600 bpm. Second, the device's settings were programmable telemetrically via a distance of approximately 5 m using a custom-built software (Fig. 1B) and a 2.4 GHz antenna (Silver S-22, Silver System, Rędziny, Poland). A unique ID was assigned to each pacemaker device such that specific communication with one device was possible although multiple devices were within the radiofrequency range. Third, the same wireless connection allowed retrieving an intraatrial ECG-signal, which was sampled via the pacemaker-probe while the stimulation was interrupted. The ECG-signal allowed distinguishing between sinus rhythm (i. e., a steady, regular, normofrequent atrial excitation) and atrial fibrillation (i. e., an irregular, high-frequent atrial excitation, see Fig. 1C).

### *Pacemaker implantation*

Sixteen female, landrace pigs (28 ± 1 kg) were sedated with an intramuscular injection of 20 mg/kg ketamine and 0.5 mg/kg midazolam, followed by 1 mg/kg propofol to allow for intubation with an endotracheal tube. Anesthesia was maintained with 1-2% isoflurane and 35 μg/kg/h fentanyl. The respirator was set to an $FiO_2$ of 40%, an I:E-ratio of 1:2, a positive end-expiratory pressure of 5 mmHg and a tidal volume of 10 ml/kg. The end-tidal carbon dioxide partial pressure was kept between 35 and 40 mmHg by adjusting the respiratory rate. The right internal jugular vein was prepared surgically via a median neck incision. A commercial pacemaker probe (Biotronik Setrox S45, Biotronik, Vienna, Austria) was implanted transvenously into the right atrial free wall under fluoroscopic guidance. The pacemaker probe was connected to the custom-built pacemaker and the stimulation threshold was determined by decreasing the stimulation width stepwise while monitoring an external ECG signal. The pacemaker was programmed to a stimulation duration of 3-fold the determined threshold. Correct placement of the probe and the pacemaker's correct function were confirmed again, the pacemaker was fixed in a pocket underneath the neck's musculature, and the neck was closed in layers using resorbable sutures. Anesthesia was discontinued and the animals were extubated. The pigs were allowed to recover from the procedure for at least 14 days. During recovery, the animals received adequate pain medication and antibiotic treatment (fentanyl transdermal system 50–100 μg/h, buprenorphine 10 μg/kg i.m., penicillin/streptomycin i.m., amoxicillin/clavulanic acid p.o.). At the same time, the oral administration of 5 μg/kg/d digoxin was started and maintained until the end of the protocol to slow atrioventricular conductance. Digoxin levels were measured in plasma samples repetitively and the dose was adjusted to maintain plasma levels of 1.0–2.5 μg/l.

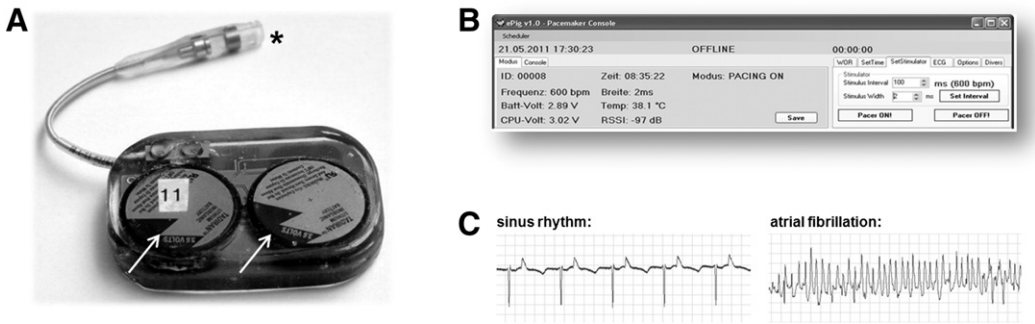


Fig. 1. The custom-built pacemaker (A) was equipped with an IS1-connector (*) compatible with commercial pacemaker probes, two lithium thionyl chloride 3.6 V batteries (white arrows) and a 2.4 GHz telemetry unit (not visible). Using a custom-built software (B) and a 2.4 GHz antenna, we were able to stream on-line intraatrial ECG-signals (C) via the pacemaker-probe to distinguish between sinus rhythm and atrial fibrillation.