Inducible lethal ventricular arrhythmias in swine with pacing-induced heart failure

Abstract Introduction: Rapid pacing-induced heart failure provides an excellent animal model for the study of heart failure. We studied the development of ventricular tachyarrhythmias using programmed stimulation in a pacing-induced heart failure model. We also studied action potential characteristics and the relationship between action potential and heart rate.

Methods and results: Ten pigs were instrumented and were studied before the onset and every week after rapid pacing was instituted. Weekly echocardiograms and programmed stimulation were done in a sedated state. In vitro electrophysiologic studies were done on left ventricular myocardium in 4 heart-failure animals and 4 controls. All animals developed progressive heart failure with left ventricular dilatation and reduced percentage fractional shortening. No arrhythmias were induced at baseline or the first and second weeks. Ventricular fibrillation was induced in one animal on the third week and 4 animals on week 4, while there was no appreciable worsening in echocardiographic indices of ventricular dysfunction between weeks 3 and 4. Ventricular effective refractory period was unchanged during the 4 weeks. In vitro studies showed action potential prolongation in heart failure myocardium. However, action potential duration at pacing rates > 100 bpm were similar to controls. No early or delayed afterdepolarizations were observed.

Conclusion: This study demonstrated an increased susceptibility to ventricular fibrillation with the development of heart failure which was not related to the degree of ventricular dysfunction. Also, the normalization of action potential duration at higher heart rates suggests that the increased incidence of inducible ventricular fibrillation in this model may not be solely due to prolonged action potential duration.

Key words Heart failure – action potential – swine – sudden death – ventricular arrhythmias

Introduction
Past studies have demonstrated that chronic rapid pacing in animals results in functional and neurohormonal characteristics which are similar to the clinical phenotype of congestive heart failure (CHF) (5, 8, 13, 18, 21–24, 26, 27). Some initial reports have examined the potential for arrhythmogenicity following the development of pacing-induced CHF (12, 17). For example, Pak et al reported that sudden death, presumably from ventricular fibrillation (VF) occurred in dogs with pacing-induced CHF (17). However, it remained unclear whether increased susceptibility to ventricular fibrillation occurs early in the progression of pacing-induced CHF and how this may be related to left ventricular (LV) function.
Accordingly, the first goal of the present study was to serially measure LV function and perform programmed electrical stimulation studies in vivo during the progression of pacing-induced CHF. Fundamental changes occur in the LV myocyte action potential with the development of CHF (2, 3, 6, 7, 12, 29). One common observation is a prolongation of the action potential duration (APD). However, a past study by Vermeulen et al. (29), demonstrated that the myocyte APD was normalized in CHF myocytes when stimulated at physiological rates. Thus, the relationship between changes in myocyte action potential morphology and the susceptibility to ventricular arrhythmias (VA) in the setting of CHF remains poorly understood. Accordingly, the second goal of the present study was to examine the potential relationship between indices of the myocyte action potential to the susceptibility to arrhythmogenesis with the development of pacing-induced CHF.

**Methods**

Ten Yorkshire pigs (6 months old, 28–30 kg, Hambone Farms, Orangeburg SC) were instrumented and, following recovery, underwent echocardiographic and programmed ventricular stimulation studies. We initially studied a group of 4 pigs after rapid atrial pacing for 3 weeks (3-week group). A second group of 6 more pigs underwent rapid atrial pacing for 4 weeks (4-week group). In the 3-week group, all animals underwent electrophysiological and echocardiographic study at baseline, and weekly thereafter after initiation of pacing. In the 4-week group, all animals were studied at baseline, 3 and 4 weeks, but only 2 animals were studied at the 1st and 2nd week. Thus, 10 pigs were studied after 3 weeks of pacing and 6 were studied after 4 weeks of pacing. Animals were treated and cared for in accordance with the National Institutes of Health guide for the Care and Use of Laboratory Animals (National Research Council, Washington DC, 1996).

**Instrumentation procedure**

The technique of implantation of the pacemaker and an aortic access port has previously been described (20). Briefly, animals were sedated with 10 mg of diazepam, intubated, and anesthetized with isoflurane (3%/1.5 L/min) and nitrous oxide (0.5 L/min). Via a left-lateral thoracotomy, a pacing electrode was sutured to the left atrial epicardium and attached to a modified pacemaker (Spectrax, Medtronics, Minneapolis MN) inserted into a subcutaneous pocket in the interscapular region. Additionally, 4 platinum leads were attached to the right ventricle and brought out together to form a common lead going to a transdermal button located in the left side of the interscapular area, away from the pacemaker and the thoracotomy. Two ventricular leads were used for obtaining intracardiac electrograms and the other two were used for weekly programmed stimulation studies. Lastly, the left internal carotid artery was exposed and a catheter attached to a vascular access port (model GPV, 9F, Access Technologies, Skokie IL). The catheter was advanced into the aortic arch and sutured into place. The access port was then buried in a subcutaneous pocket over the thoracolumbar fascia.

Following a 2-week period of recovery, a baseline echocardiographic and programmed stimulation study was performed, after which the pacemaker was turned on to pace the atrium at 240 bpm. This rate was chosen because it represents an approximate doubling of the normal heart rate in these animals and had been previously shown to reliably lead to CHF in 3 weeks (20, 25).

**Study protocol**

The pigs were pre-sedated with diazepam (10 mg) and brought to the laboratory in a sling. The vascular access port was entered using a 12-gauge Huber needle attached to a saline-filled tube and a Statham 23ID (Gould, Oxnard CA) pressure transducer. Further sedation was achieved with 5 to 10 mg boluses of midazolam given through the vascular access port. Surface electrocardiographic electrodes were attached to each limb, and standard electrocardiogram leads 1, 2 and 3 were displayed on a physiologic recorder (EVR-16, Electronics for Medicine, Overland Park KS), along with the intracardiac ventricular electrogram. The pacemaker was then turned off. Following a 30-minute equilibration period, a two-dimensional and M-mode echocardiographic study of the LV function was performed (ATL Ultramark VI, 2.25 MHZ transducer, Bothell WA) from the right parasternal approach. LV dimensions were measured and fractional shortening was calculated.

**Programmed stimulation protocol**

Ventricular stimulation was performed using a Medtronics stimulator (Model 5328, Medtronics, Minneapolis MN). Recordings were made at 25 mm/s paper speed on the physiologic recorder at standard filter settings. The ventricular excitation threshold was measured and stimulation strength was set at twice diastolic threshold. Following an 8-beat train at a basic cycle length (BCL) of 300 ms, a single extrastimulus was introduced late in diastole (starting at 280 ms) and decremented in 10 ms steps until loss of ventricular capture. Ventricular effective refractory period was defined as the longest S1S2 interval at which S2 failed to achieve ventricular excitation. Then, double extrastimuli were introduced with both S2 and S3, initially at 50 ms longer than the ventricular