Pacemaker-induced cardiomyopathy in the sheep: RVA but not RVOT pacing results in a heart failure cellular phenotype.

GJ Kirkwood MBBS PhD, M Lawless PhD, C Pearman MBBS PhD, E Radcliffe, J Caldwell, AW Trafford PhD

Department of Cardiac Physiology, University of Manchester, UK
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Abstract

Chronic RV apical pacing can have adverse effects on LV function and up to 10% of patients develop Pacemaker-induced Cardiomyopathy. The pathophysiology of this is incompletely understood, although previous work has shown that altered ventricular activation patterns can cause abnormal calcium handling and apoptosis. The aim of this work was to determine whether physiological-rate RV apical pacing could cause a cellular heart failure phenotype and if this could be prevented by pacing from the RV outflow tract (RVOT).

Methods

Experiments were performed in adult female Welsh Mountain sheep, in accordance with national regulations and local ethical review. Under general anaesthetic and fluorescent screening, transvenous pacing leads (Medtronic Novus 4076) were implanted via the right internal jugular vein and attached to a generator positioned in a cervical pocket. After 1 week to recover from surgery, pacing was commenced according to the experimental model.

RV pacing Model

Leads were positioned in the right atrial appendage and either RV apex or RVOT. These were connected to a Medtronic Sensia dual chamber pacemaker.

Heart Failure Model

A single lead was positioned at the RV apex. This was connected to a Medtronic Consulta implantable defibrillator. A high rate pacing program provided by the company allowed continuous ventricular pacing at a rate of 210 bpm, which is approximately double the normal resting heart rate in the sheep. This resulted in tachycardia-induced cardiomyopathy developing over 4 – 6 weeks. Animals were sacrificed when they displayed clinical symptoms of end-stage heart failure (palor, lethargy and pulmonary oedema).

Background

Right ventricular apical (RVA) pacing can be detrimental to cardiac health. Although most apparent with pre-existing heart failure, chronic pacing can also cause heart failure in patients with previously normal ventricular function.

Pacemaker-Induced Cardiomyopathy (PiCM) affects up to 10% of patients with high RV pacing burdens within 1 year of implantation. This causes deterioration of left ventricular (LV) function and may be associated with symptoms of heart failure. These changes are largely reversible by cardiac resynchronisation therapy.

Mechanisms for PiCM are only partially understood. This is likely to result from abnormal wall stress within the LV. Pacing from the RV apex alters the LV activation pattern, which can result in stretching and delayed contraction of the LV free wall. This reduces the mechanical efficiency of LV contraction and may identify patients at risk of developing PiCM.

Short-term alterations in ventricular activation result in cellular changes that underlie the phenomenon of cardiac memory, including an increased calcium transient magnitude in late-activated regions, but these do not necessarily result in heart failure. Changes associated with heart failure are likely to result from reduction of L-type calcium current (I_{Ca,L}). These features were not observed with RVOT pacing.

Isolated Cardiomyocyte Studies

After death, cells were isolated from the mid layer of the LV free wall using enzymatic digestion and loaded with the ratiometric calcium indicator Fura-2 AM. The perforated patch current clamp technique was used to study the steady-state triggered calcium transient. Whole cell voltage clamp studies were performed to measure L-Type calcium current (I_{Ca,L}). Studies were performed in Tyrode’s solution with 1.8 mM [Ca^{2+}] at 37°C. In selected animals, cardiomyocytes were stained with di-4 ANPEPS and studied with confocal microscopy to examine the transverse tubule structure. Experimental animals were compared with uninstrumented controls, matched approximately for age and weight.

Conclusions

3 months of physiological rate RV apical pacing resulted in a heart failure cellular phenotype, characterized by calcium transient abnormalities and T-tubule disruption. These features were not observed with RVOT pacing.

These findings occurred before clinical or echocardiographic features of heart failure and may therefore represent the initial stages of Pacemaker-induced Cardiomyopathy.

References

1. Yu et al. (2009), NEJM 361:2123-34

graeme.kirkwood@manchester.ac.uk