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

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Supported by research fellowships from the British Heart Foundation

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).

Adult sheep were paced at physiological heart rates for 3 months from the RV apex or RVOT. Another group underwent rapid ventricular pacing to cause tachycardia-induced heart failure. Cardiomyocytes from the LV free wall were studied using patch clamp techniques and confocal microscopy.

RV apical pacing caused a cellular phenotype similar to heart failure, with attenuation of the calcium transient, reduction of $I_{Ca\text{-}L}$ and disruption of T-tubules. These features did not occur with RVOT pacing.

Changes appeared prior to clinical or echocardiographic evidence of heart failure and may therefore represent the initial stages of Pacemaker-induced Cardiomyopathy.

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 implant[1]. 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, but are 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.

S*hort-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[2]. However, there is no data as to how this may relate to the *long-term* development of PiCM, in particular as heart failure typically causes dramatic attenuation of the calcium transient[3].

Furthermore, no studies have investigated the cellular effects of chronic pacing from the RV outflow tract (RVOT). This is generally considered to give a more 'physiological' electrical activation pattern, although this does not result in consistent clinical benefits.

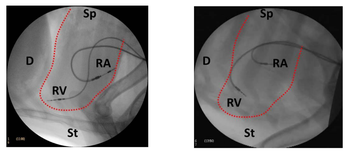
To address these aspects, we developed a novel sheep model of chronic physiological rate RVA pacing. We studied cellular calcium handling to determine whether changes previously described in tachycardia-induced cardiomyopathy may also underlie PiCM, and whether these could be prevented by pacing from the RVOT.

Methods

Experiments were performed in adult female Welsh Mountain sheep, in accordance with national regulations and local ethical review. Under general anaesthetic and fluoroscopic 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.



Fluoroscopic RAO projections demonstrating RVA (left) and RVOT (right) lead positions. Septal orientation was confirmed using LAO projections.

D: Diaphragm Sp: Spine St: Sternum

Pacing was performed in VDD mode. The sensed AV delay was adjusted between 30-50ms to give 100% RV pacing with no fusion beats. Pacing continued for 3 months, during which time animals displayed no clinical symptoms.

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 (pallor, lethargy and pulmonary oedema).

Animals from both groups underwent weekly ECG and transthoracic echocardiographic examinations. Rapid ventricular pacing resulted in LV dilatation and loss of contractile function with the development of resting tachycardia. These changes did not occur with either RV pacing model.

Isolated Cardiomyocyte Studies

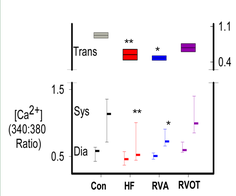
After death, cells were isolated from the mid layer of the LV free wall using enzymatic digestion and loaded with the ratiometric calcium indicator Fura-2AM. The perforated patch current clamp technique was used to study the steady-state triggered calcium transient. Whole cell voltage clamp studies were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

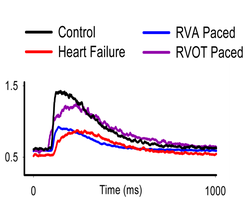
Figures are presented as mean +/- SEM where normally distributed, otherwise as median/ IQR. Statistical significance was tested using ANOVA/ ANOVA by ranks.

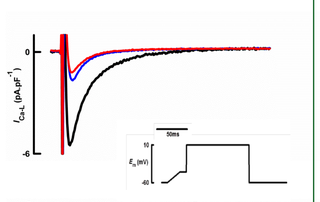
Group sizes 6-18 subjects, 8-24 cells

Results

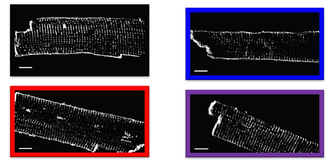
RVA but not RVOT pacing causes a heart failure cellular phenotype



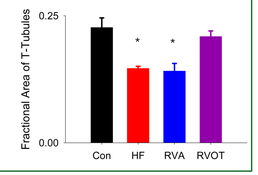




*Systolic peak [Ca^{2+}] and calcium transient magnitude were reduced in heart failure and after RVA pacing (left). This appeared to result from reduction of $I_{Ca\text{-}L}$ (right). *p<0.05, **p<0.005*



RVA but not RVOT pacing caused disruption of T-tubule structure, similar to that seen in heart failure.



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

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3. Briston et al. (2011), *J Physiol 589(Pt 6):1367-82*
4. Caldwell et al. (2014), Circ Res 115(986-996)

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