Objective

To investigate the differential electrophysiological roles of $\beta_1$ vs $\beta_2$ adrenergic (AR) stimulation on regulating pacemaker activity in the isolated right atrium of a large mammalian model.

Introduction

Excessive $\beta$-AR stimulation is a hallmark of heart failure (HF) [1]. In the development of end-stage HF, cardiac output is reduced and myocardial function declines. The sympathetic nervous system compensates for these losses by activating $\beta$-AR receptors and thus increasing heart rate and cardiac contractility [2]. Specifically, circulating catecholamine levels rise to regulate G-protein-coupled receptor activity and hemodynamic demands. Acutely, $\beta$-AR receptor activation can effectively return cardiac conditions back to normal levels; however, chronic sympathetic activity may be deleterious to the heart and actually lead to further pathologic changes and deterioration of both cardiac structure and function [2].

There are two dominant subtypes of $\beta$-AR: $\beta_1$ and $\beta_2$. The signaling and functional properties of these two adrenergic receptors are distinctly different (Fig. 1). $\beta_1$-AR mediates chronotropic and inotropic effects of catecholamines via the stimulatory $G$ protein (Gs), whereas $\beta_2$-AR can couple to both Gs and the inhibitory $G$ protein (Gi) [2].

Background & Motivation

$\beta$-blockers are a mainstream therapy for many of those who suffer from heart failure, but it is not fully understood how $\beta$-AR stimulation directly affects pacemaker activity. Recent studies have shown that stimulation of $\beta_1$- and $\beta_2$-AR has varying electrophysiological responses and arrhythmogenic effects on the heart, specifically in the ventricles (Fig. 2) [1]. Therefore, it was the goal of this study to examine the electrophysiological roles of $\beta_1$- vs $\beta_2$-AR stimulation on the right atrium of a large animal model to better understand their differential effects in regulating pacemaker activities.

Methods

Figure 3. Schematic representation of dual-sided optical mapping setup. Isolated canine right atrial preparation is placed in a temperature controlled bath at 37°C and perfused with oxygenated Tyrode solution. The tissue is suspended vertically to allow optical access to both endocardial and the epicardial surfaces. Each side of the preparation is excited with a 520-nm LED light source, and emitted fluorescence captured through a 690-nm long-pass filter using two MICAM Ultima-L CMOS cameras facing eachother with the same 5×5 cm field of view. Recordings were captured at 1000 Hz.

Figure 4. Representative views of epicardial (left) and epicardial (right) surfaces of the isolated canine right atrium. SAN indicates sinoatrial node; CT, crista terminals; RA, right atrium; RV, right ventricle; IS, interatrial septum; RCA, right coronary artery (cannulated).

Figure 5. Detailed timeline of the experimental protocol. Specific agonists for $\beta_1$-AR and $\beta_2$-AR (propranolol at 1μmol/L and sotalol at 1μmol/L, respectively) were perfused into the preparation. Agonists were applied at saturating concentrations according to previous cardiac studies [1] so that the maximum effective activation of the receptors could be achieved.

Figure 6. Representative activation maps of the isolated canine right atrium upon pharmacological stimulation of $\beta_1$- and $\beta_2$-AR.

Figure 7. Changes in average heart rate and APD80 with sympathetic pharmacological stimulation.

Conclusions

- This data shows, for the first time, a differential electrophysiological role of $\beta_1$ and $\beta_2$ in right atrial tissue of a large animal model.
- Both $\beta$-ARs increase automaticity of pacemaker tissue, but $\beta_2$ has a larger impact than $\beta_1$ in decreasing APD80.
- Dual-sided optical mapping is beneficial for showing shifts in the leading pacemaker initiation sites in the presence of adrenergic agonists.
- In contrast to effects observed in normal ventricular tissue, $\beta$-AR subtypes play opposing roles in regulating action potential duration in the right atrium.
- The results of this study offers new insights into the differential role of $\beta_1$ and $\beta_2$ in regulating heart rate and the propagation of electrical activity throughout pacemaking tissue.

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References