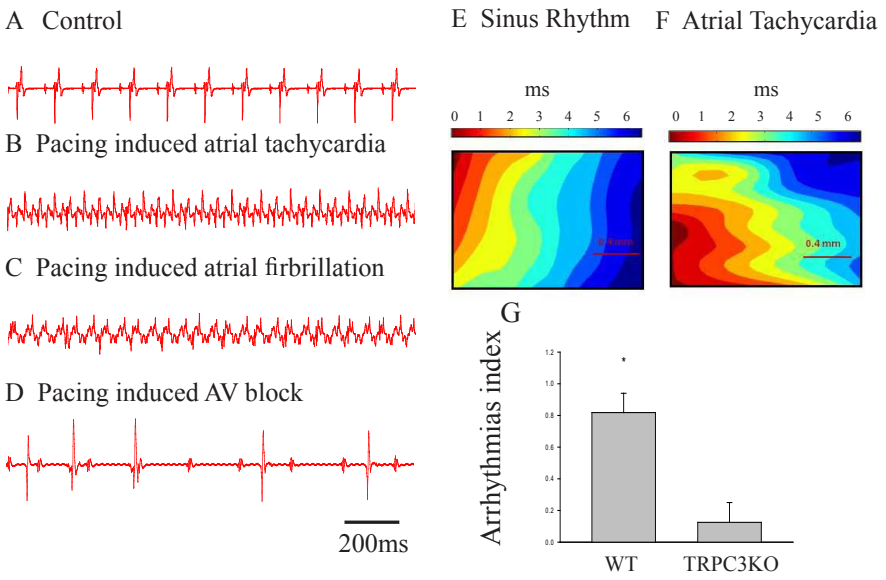
The involvement of TRPC3 channels in sinoatrial arrhythmias

Y.K. Ju,[1] M. Lei,[2] S. Trajanovska,[1] G. Hao[2] and D.G. Allen,[1] [1]School of Medical Sciences, Bosch Institute, University of Sydney, NSW 2006, Australia and [2]The Department of Pharmacology, University of Oxford, UK.

Recent evidence suggests that Ca^{2+} entry through the Transient Receptor Potential Canonical-3 (TRPC3) channel is related to pathological heart disease, including cardiac hypertrophy (for review see Eder & Molkentin, 2011). TRPC3 is also involved in cardiac arrhythmias such as atrial fibrillation (Harada *et al.*, 2012). TRPC3 channels carry non-selective cation current and are directly activated either by agonist such as angiotensin II (AngII) which bind to G protein–coupled receptors or by diacylglycerol (DAG) (for review see Birnbaumer, 2009). However, the functional role of TRPC3 in regulation of cardiac rhythm and the mechanism of TRPC3 involvement in arrhythmogenesis remain largely unknown.

We previously found that sinoatrial and atrial cardiac myocytes express TRPC3 (Ju *et al.*, 2007). To investigate the possible involvement of TRPC3 in sinoatrial arrhythmias, we first studied the electrophysiological properties of Langendorff-perfused hearts from WT and TRPC3 KO mice implanted with angiotensin II (AngII, 2 μg/g/day) mini pumps for 10-12 days. Electrical activity was recorded with two mini monopolar ECG electrodes placed on the atria and ventricle (Figure A). Sinoatrial arrhythmias including atrial tachycardia, atrial fibrillating and sinus bradycardia were induced by burst electrical pacing (as showed in Figure B-D). To determine the electrical conduction velocity in the sinoatrial region, custom-made electrode arrays were used to record electrical activity from isolated Langendorff-perfused hearts. Activation maps that show the origin of excitation and the conduction velocity were changed during arrhythmic events compare to the regular sinoatrial rhythm (as shown in Figures E & F). We found that the sinoatrial arrhythmias induced by AngII and pacing were reduced in the TRPC3 KO mice. On average, the arrhythmia index was significant reduced in TRPC3 KO mice groups (n = 8) compared to WT group (n = 11, p = 0.004, Figure G).



To further investigate the role of TRPC3 in sinoatrial arrhythmias we recorded sinoatrial action potentials in isolated mouse sinoatrial complexes. Firing rates were increased and membrane potentials were depolarised in the presence of AngII (1 μM) and DAG (100 μM). The effects of AngII and DAG were blocked by a specific TRPC3 channel blocker PYR10 (2-20 μM). Our results suggested that the sinoatrial arrhythmias caused by G-protein coupled receptor activation may involve an inward current activated through TRPC3 channels.

Birnbaumer L. (2009) *Annual Review of Pharmacology and Toxicology* **49**, 395-426.

Eder P & Molkentin JD. (2011). *Circulation Research* **108**, 265-272.

Harada M, Luo X, Qi XY, Tadevosyan A, Maguy A, Ordog B, Ledoux J, Kato T, Naud P, Voigt N, Shi Y, Kamiya K, Murohara T, Kodama I, Tardif JC, Schotten U, Van Wagoner DR, Dobrev D, & Nattel S. (2012) *Circulation* **126**, 2051-2064.

Ju YK, Chu Y, Chaulet H, Lai D, Gervasio OL, Graham RM, Cannell MB, & Allen DG. (2007) *Circulation Research* **100**, 1605-1614.

This research is supported by NH&MRC , TRPC3 KO mice are provided by Prof. Gary Housley.