

## The molecular architecture of the heart's conduction system in health and disease

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The cardiac conduction system (CCS) acts as the heart's wiring system and is vital for the initiation and coordination of the heart beat (Boyett, 2009). The main tissues comprising the CCS are the sinoatrial node (the pacemaker of the heart), atrioventricular node (responsible for slow action potential conduction from the atria to the ventricles and, thereby, a delay between atrial and ventricular systole) and the His-Purkinje system (responsible for fast action potential conduction throughout the ventricles and, thereby, the synchronised contraction of the ventricles) - they were discovered in the late 19<sup>th</sup> and early 20<sup>th</sup> centuries. The electrical activity of the CCS is ultimately dependent on the expression of ion channels and, using quantitative PCR and immunohistochemistry, we are mapping the expression of ~80 ion channel subunits in the CCS (*e.g.* Chandler *et al.*, 2009). Unsurprisingly, the expression pattern is very different from that in the working myocardium, but appropriate to explain the electrical activity of the CCS. For example, pacemaking in the sinoatrial node can be explained by the poor expression of the background K<sup>+</sup> channel, K<sub>ir</sub>2.1, the expression of the pacemaker ion channel, HCN4, and perhaps the high expression of the low voltage-activated Ca<sup>2+</sup> channels, Ca<sub>v</sub>1.3 and Ca<sub>v</sub>3.1; slow conduction through the atrioventricular node can be explained by the poor expression of the major Na<sup>+</sup> channel, Na<sub>v</sub>1.5, and the major gap junction channel, Cx43; fast conduction through the His-Purkinje system can be explained by the high expression of Na<sub>v</sub>1.5 and expression of the large conductance gap junction channel, Cx40. The heart rate of the mouse is about 100× faster than that of the human and this can be explained by differences in ion channel expression: analysis suggests that channels carrying outward current are generally more highly expressed in the mouse sinoatrial node and this is expected to result in a shorter action potential (essential in the case of a higher heart rate) and channels carrying inward current are also generally more highly expressed in the mouse sinoatrial node and this may be responsible for the faster heart rate of the mouse.

There is dysfunction of the CCS in the aged heart, in heart failure (HF), atrial fibrillation and possibly diabetes (Boyett, 2009). For example, a substantial proportion (~16%) of HF patients die of bradyarrhythmias and there is dysfunction of all parts of the CCS in HF: there can be sinus bradycardia and prolongation of atrioventricular nodal conduction and heart block, and ~26% of HF patients have left bundle branch block. We and others are showing a widespread remodelling of ion channels in the CCS in heart failure – for example, in a rat model of heart failure (following pulmonary hypertension), 14 out of 21 transcripts for ion channels and related proteins were altered in the sinoatrial node (the CCS appears peculiarly sensitive to HF – for example, in this model only 4/21 transcripts were altered in the atrial muscle. The dysfunction of the CCS in disease is likely to be the result of the remodelling of ion channels - for example, the sinus bradycardia in HF and atrial fibrillation has been attributed to a downregulation of HCN4 in the sinoatrial node (Boyett, 2009). There is even evidence of 'dysfunction' in trained athletes: sinus bradycardia, prolongation of atrioventricular nodal conduction and heart block and incomplete right bundle branch block. The effects of athletic training have been attributed to 'high vagal tone', but there is no evidence for this and instead it is more likely to be the result of a remodelling of ion channels (Boyett, 2009). The CCS is more extensive than originally thought and specialised nodal-like tissue encircles the tricuspid and mitral valves, pulmonary artery and aorta and is potentially responsible for atrial tachycardias and ventricular outflow tract tachycardias (Boyett, 2009).

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