In this issue Tellez et al\(^1\) give a detailed analysis of differentially expressed genes regulating excitation and conduction in the sinoatrial node (SAN) in rabbit. Quantitative PCR and in situ hybridization, as well as action potential recordings, enabled the investigators to assign specific patterns to central and peripheral regions of SAN, and to compare these with the corresponding properties of atrial tissue. Cluster analysis revealed that the SAN transcript profile is significantly different from that of atrial muscle. More importantly, there are apparent isoform switches on moving from atrial muscle to the SAN center: RYR2 to RYR3, Na\(_{1.5}\) to Na\(_{1.1}\), Ca\(_{1.2}\) to Ca\(_{1.3}\) and K\(_{1.4}\) to K\(_{4.2}\). In this context the transcript profile of the SAN periphery represents an intermediate pattern between that of central SAN and atrial muscle.

Differential expression of a variety of genes has been demonstrated in anatomically distinct regions of the heart, for example atrial versus ventricular myocardium,\(^2\) or ventricular endocardium versus ventricular epicardium,\(^3\) which gives clues to the molecular substrates controlling distinct myocardial electrical properties of specific regions in the heart.

Tellez et al meticulously dissected SAN tissue based on previous work and functional studies, and the authors were able to demonstrate that differential expression corresponds to specific electrical properties of SAN central, SAN periphery and free atrial myocardium. SAN central is characterized by poor electrical coupling to protect against inhibitory hyperpolarizing influence of surrounding atrial muscle. It provides ionic currents appropriate for pacemaking, resulting in spontaneous activity, a pacemaker potential, low take-off potential of the action potential, slow upstroke, small overshoot, small amplitude, long duration, low maximum diastolic potential (MDP). SAN periphery (specifically, the anatomically defined right branch of the sinoatrial ring bundle [RSARB]) has strong electrical coupling, ionic currents composed of higher take-off potential of the action potential, faster upstroke (25-fold), large amplitude and short duration with a high maximum MDP. SAN periphery serves to insulate SAN central from atrial myocardium on the one hand, and to conduct and propagate impulses to atrial tissue on the other hand.

**Tuning Conductance**

Differential expression of gap junction proteins is a major factor controlling the extended conduction system and has recently been described by this group in detail.\(^4\) In SAN central and SAN periphery, gap junction protein expression corresponds to differences in electrical coupling. Whereas messenger RNA for Cx43, a medium conductance gap junction protein, is abundant in atrial myocardium, (present in SAN periphery but absent in SAN central) messenger RNA for Cx45 (and 30.2), a low conductance gap junction protein, is present in SAN central.

**Tuning Pacemaking**

The importance of SR Ca\(^{2+}\) release in SAN pacemaker rate, and response to \(\beta\)-adrenergic activation, has recently been substantiated by Bogdanov et al\(^5\) and highlighted by an editorial by Bers\(^6\) in this journal. Differences in intracellular Ca\(^{2+}\) handling between the center and the periphery of the rabbit SAN may be related to the observed isoform switch from RYR2 to RYR3, from atrial muscle to SAN central. The isoform switch from Ca\(_{1.2}\) to Ca\(_{1.3}\), from atrial muscle to SAN center with Ca\(_{1.3}\) activating at more negative potentials than Ca\(_{1.2}\) is another example for fine tuning the pacemaking and corresponds to the absence of Na\(_{1.5}\) messenger RNA in SAN central but not in SAN periphery and surrounding atrial muscle.

**Future Tuning**

A century past the discovery of the pacemaker of the heart\(^7\) and half a century past the first functional studies of the rabbit sinoatrial node,\(^8\) building on the wealth of previous studies of sinus node physiology in rabbit, we are reaching a level of detailed understanding that challenges us to compile a comprehensive model with qualitative and quantitative signaling. This will help our understanding of malfunction or loss of sinus node pacemaker cells because of disease or aging, and will direct us toward more sophisticated cures. Very recently, bioartificial pacemaker have been designed successfully to modulate excitation either by transfer of a key pacemaker channel\(^9\) or by a synthetic pacemaker channel\(^10\) designed to minimize interference with intrinsic ion channels and maximize flexibility with regard to frequency tuning.

In addition detailed analysis of rare model diseases, such as familial sick sinus syndrome that has been linked to loss of function mutations in SCN5A, the gene encoding Nav1.5 may help to focus our attention on key elements of pacemaking and conduction.\(^11–14\) On the other hand, these rare model

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diseases may help to comprehend the pathology and potential genetic susceptibility to the more common forms of sinus node dysfunction and conduction disease. In this context the complexity of our current understanding of sinus node physiology asks for a more complex polygenic substrate even in many cases that are currently viewed as monogenic.

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References

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Tuning the Beat: Differential Expression of Ion Channels in the Sinus Node

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