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Perspectives

PERSPECTIVES

# Metabolic Control of Cardiac Pacemaking

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## A Perspective on "The Organization of the Sinoatrial Node Microvasculature Varies Regionally to Match Local Myocyte Excitability"

The function of the heart is to pump blood and meet the physiological needs of all organs in the body. In healthy young adults, the heart rate exhibits an impressive 4-fold dynamic range of about 60 beats per minute (bpm) at rest to up to ~200 bpm during exercise and/or stress. Heartbeats originate in the sinoatrial node (SAN), a special collection of cells at the junction of the right atrium and the superior vena cava, where the electrical pacemaker signal arises at a rate governed by diverse inputs. The action potential (AP) is then conducted throughout the heart to activate contraction. A growing body of evidence suggests that the SAN is not homogeneous since the dominant site of pacemaking activity within the structure shifts in response to physiological stimuli.[1] An intriguing question is how the structural and functional heterogeneity of discrete SAN subregions and SAN cells may interact and lead to periodic and dynamic control of the heart rate. Notably, the role of the SAN vasculature in pacemaking has been largely ignored, as has the nature of the signaling between the SAN cells and the microvasculature of the heart.

These issues are raised by Grainger and co-workers in their investigation of the influence of the local vasculature on the SAN that appears in *Function*[2] This study used high-resolution 3D imaging to reveal the microanatomy of the murine SAN and used patch-clamp electrophysiology and $Ca^{2+}$ imaging to elucidate operative distinctiveness in subsets of SA nodal cells. The findings provide insight into the relationship between SAN regional coronary blood supply and the spontaneous electrical excitability of SAN myocytes, describe specific functional properties of cells from different SAN subregions, and promote a recently proposed bistable model of cardiac pacemaking.[3,4]

Evidence supporting the concept that the origination site of electrical activity in the heart is plastic has been reported over several decades,[1] but the mechanistic basis for this phenomenon remains poorly understood. A recent important study by Brennan et al. addressed this topic and provided evidence of two specific SAN regions in the hearts of rodents and humans that were designated as the superior and inferior SANs (sSAN and iSAN) based on their relative anatomical localization.[5] Using high-resolution optical mapping of membrane potential changes in intact SANs, the authors provide evidence that in the rat heart, the sSAN acted as the primary pacemaker at higher heart rates, whereas the iSAN predominated at lower rates.

Building on these findings, Grainger and colleagues co-immunolabeled murine hearts for HCN4 and CD31 to identify SAN myocytes and endothelial cells, respectively. Excellent 3D images revealed that the sSAN was highly vascularized, and individual HCN4-positive cells appeared to be in more intimate contact with blood vessels compared with the iSAN. Comparison of the electrophysiological and $Ca^{2+}$ signaling properties of individual SAN myocytes revealed pronounced region-specific differences, including higher rates of spontaneous APs in cells from the sSAN and a large proportion of iSAN cells that produced few APs but spontaneously generated subthreshold voltage oscillations. The authors put forth the idea that the sSAN is highly vascularized to support the energetic demands of cells generating APs at a higher frequency. However, given the modest energy resources needed to service electrical activity of the SA nodal cells compared to the huge requirements of contractile atrial and ventricular myocytes, we suggest that the ATP consumption by SAN cells should be mea-

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sured quantitatively with explicit calibration that may not have been possible ten years ago.[6] Nevertheless, more work exploring the metabolic regulation of blood flow in the heart is a hot topic and widely considered essential for a broad understanding of cardiac physiology and disease.[7] As the current study makes clear, such an investigation is important for a deeper understanding of the molecular and cellular physiology of SAN cells.

### Future Work

We are left with some challenging and unanswered questions for the next stage of SAN investigations. A detailed analysis of blood flow regulation at the SAN capillary level under various physiological conditions will directly address the possibility that the delivery of energetic substrates and metabolic regulation and underlie the observed inhomogeneity in SAN electrical activity. How do the small vessels that supply the SAN cells communicate to regulate the local blood flow? Could they connect electrically through gap junctions[7] as has been suggested for ventricular myocytes? If the intracellular ATP concentration within the SAN cells were to decline, this would be expected to increase the activity of ATP-sensitive $K^+$ channels and thus hyperpolarize the time-averaged pacemaker cells, which are in metabolic need of greater blood flow. Under such conditions, the intrinsic AP rate of these cells would be slowed. Could this mechanism contribute to the functional differences observed in the sSAN region vs the iSAN region? Further, can superresolution imaging methods be used to broaden our understanding of the distinction of $Ca^{2+}$ sparks[8,9] vs the concept of "local $Ca^{2+}$ releases"? In other words, are type 2 ryanodine receptor (RyR2) clusters uniquely organized at the nanoscale in SAN cells, or are they similar to the organization reported for atrial cells?[10] Are RyR2 clusters arranged differently in the sSAN compared with the iSAN? This is an important question, as minor differences in RyR2 clusters size can change during disease and significantly influence membrane excitability.[11] Finally, studies that consider the consequences of blood flow regulation within the SAN in the context of arrhythmic disease are critical.

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## Disclosures

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