Editorial

Aging and Sinoatrial Node Dysfunction
Musings on the Not-So-Funny Side

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In the century since the discovery by Keith and Flack of the sinoatrial node in the mole heart, a detailed mosaic of its cellular, anatomic, and electrophysiological properties has emerged. The human sinus node has been found to be anatomically constant and well localized, occupying an approximately 10-mm subepicardial region on the sulcus terminalis at the superior cavo–atrial junction. Histologically, its ultrastructure of central P cells (likely corresponding to the leading pacemaker site) and outer transitional zone merging with surrounding atrial myocardium have been well characterized. Great progress also has been made in defining the ionic mechanisms responsible for the sinoatrial action potential and its spontaneous pacemaker activity, including important contributory roles for $I_{Ca-L}$, $I_{K}$, and the funny current, $I_{f}$. This morphologically discrete, unifocal sinus node is not the exclusive force behind clinical sinus rhythm, however. Detailed animal and human mapping has demonstrated that normal cardiac pacemaker activity is widely distributed in the right atrium. In the human atrium, the pacemaker complex extends for up to 75 mm along the long axis of the sulcus terminalis and precaval band. At times, even left atrial pacemakers may be active during normal sinus rhythm. Graduated differential sensitivity to adrenergic and vagal inputs exists along the integrated pacemaker complex such that superior sites tend to dominate during periods of sympathetic drive, whereas inferior sites are activated by increased parasympathetic tone. Increasing the complexity, each sinus beat may have multicentric origin, and the nature of conduction out of the node also seems to be variable in response to autonomic tone. The presence of a diffuse pacemaker complex in humans is supported not only by mapping studies but also by experience with catheter ablation of the sinus node. To achieve successful reduction of sinus rate, frequently extensive ablation along a large segment of the pacemaker complex is required. Furthermore, the difficulty in achieving successful long-term reduction in sinus rate after ablation may be viewed as a testament to the nonlocalized, redundant nature of the atrial pacemaker complex.

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Sick sinus syndrome, first described as a clinical entity almost 4 decades ago, is the most common indication for bradycardia-related permanent pacing, and its prevalence is projected to increase as the population ages. It is important to note that the characterization of an extensive atrial pacemaker complex has changed our conception of the pathophysiology underlying and necessary for the development of sinus node dysfunction (SND). Sanders et al have demonstrated that patients with clinical SND do have evidence of diffuse atrial structural remodeling involving most regions of the right atrium. Many of these changes were particularly marked along the long axis of the crista terminalis, where extensive fractionated electrograms, double potentials, and slowed conduction were observed together with a marked reduction in voltage amplitude. This latter observation may be a marker for regional fibrosis, but histological corroboration was lacking. This structural remodeling was frequently associated with caudal migration of atrial pacemaker activity to the inferior region of the sulcus terminalis and a localized unicentric site of the earliest activity. These observations suggest that development of a diffuse atrioatriopathy is necessary for clinical SND to be manifest.

Indeed, similar but less marked atrial remodeling has been shown in association with human aging in patients without structural heart disease or atrial arrhythmias, who do not (yet) have clinical manifestations of SND. In that study, by Kistler et al, aging was associated with conduction slowing and voltage loss that, although diffuse, was particularly marked around the region of the crista terminalis, together with electrophysiological evidence of a decrease in sinus node reserve. The study by Kistler et al has demonstrated that subclinical loss of sinus node function in an otherwise healthy, aged population can be accompanied by widespread changes in the atrial electrical substrate. However, it is not understood why these manifestations are silent in the majority of people, whereas in others, they result in the development of clinical SND. The presence of other factors such as ischemia, cardiac failure, or other causes of atrial stretch and remodeling may play an important contributory role. Reduction in sinus node reserve has been shown to occur in congestive cardiac failure and in the presence of chronic right atrial stretch associated with an atrial septal defect. Both of these conditions also demonstrate the type of diffuse atrial structural remodeling described above.

Furthermore, the diffuse atrioatriopathy of aging provides a mechanism not only for SND but also for the commonly associated atrial arrhythmias and, in particular, atrial fibrillation, which will develop in up to 50% of patients with SND. In addition, the development of atrial fibrillation may further exacerbate SND. This effect seems to be secondary to high atrial rates, and at least partial reversal of this adverse sinus node remodeling may occur after successful catheter ablation of atrial fibrillation or atrial flutter.
Whereas clinical investigation of SND can only focus on the gross electrophysiological and structural changes detectable with mapping techniques, the study by Jones et al.14 in this issue of Circulation provides an important insight into the molecular mechanisms underlying the senescent loss of sinoatrial node function. In a guinea pig sinus node model, the authors show progressive downregulation of sinus node \(I_{Ca,1}\) expression from an early age, commencing in the central zone at the leading pacemaker site. This process continued with increasing age until peripheral sinus node zones were also involved, ultimately reducing the depolarization reserve and excitability of the pacemaker complex.

Previously, these investigators have also demonstrated increasing electrical disconnection of the guinea pig sinus node with aging, due to loss of connexin-43 expression in both the central and peripheral zones of the sinus node.15 The 2 studies together provide a mechanism both for age-related reduction in sinus automaticity and impaired sinus node conduction.

Perhaps surprisingly, in the context of clinical mapping studies, the authors found no changes in collagen content or signs of fibrosis associated with aging in this guinea pig sinus node model. Similarly, Alings et al.16 found that although the relative volume of collagen in the human sinoatrial node increased from childhood to adulthood, no further increase occurred once adulthood had been reached. Other studies have shown that in humans, aging is associated with increasing conduction anisotropy in the atrium that, histologically, was associated with increasing collagen.17 The development of generalized atrial fibrosis does not necessarily implicate the sinus node region, and further studies in humans are necessary to settle this issue.

Although the study by Jones et al.14 does not address down-regulation of \(I_{Ca,1}\) at other atrial sites, this has been documented in a senescent cellular canine model.1.18 Such global reduction in Ca,1.2 suggests, again, a generalized process of senescent electrical and structural remodeling, of which SND and atrial fibrillation are the 2 most visible clinical manifestations.

Interestingly, Jones et al.14 describe a negative chronotropic effect of nifedipine on the leading pacemaker site; this was more marked in the aged sinus nodes. This result is concordant with previous reports of the effects of topical nifedipine in isolated sinoatrial node preparations, underscoring the importance of the \(I_{Ca,1}\) in action potential upstroke in this zone of the sinus node. The clinical implications of this observation are unclear, however. One clinical report found no adverse effect on sinus node function with clinical doses of nifedipine given to patients with SND after pharmacological autonomic blockade.19 Similar data exist for the closely related dihydropyridine Ca,1.2 antagonist amlodipine.20

The study by Jones et al.14 adds greatly to our current conceptualization of SND. It increasingly seems that, apart from their clinical association, SND, atrial fibrillation, and aging are fundamentally connected at a mechanistic level. Changes in sinoatrial ion channel expression and development of widespread atrial structural remodeling may both play roles in the development of these common conditions in the aging heart.

Disclosures

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References


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