For me, it takes only a short bout of insomnia to trigger an acute awareness and reflection on the pacemaker mechanisms of the heart. In my quiet wakefulness, attempting to suppress vexing thoughts of grant deadlines, perplexing experimental results, or various other items, I often focus on counting heartbeats rather than sheep. How can the pacemaker deliver more than 90 thousand beats per day, 365 days a year for more (hopefully many more) than 70 years straight? What was that stray irregularity in the rhythm I just noticed? Can I consciously change the rate? Undoubtedly, the heartbeat is the preeminent biological oscillator that pervades our thoughts, inspires our literature, and even defines our perception of time. Thus, 100 years after the anatomic and functional descriptions of the pacemaker regions of the heart, we continue to be fascinated by the mechanism of spontaneous self-organization, occurring in both time and space, of these robust cardiac timekeepers.

With the advent of improved tissue-based and cellular electrophysiological methods in the 1960s and 1970s, a plethora of information about the ionic currents and modulators of cardiac pacemakers became available, and the field progressed toward an integrated understanding of the relationship between different ion channel properties (eg, the selectivity and gating kinetics) and oscillatory dynamics, guided by the seminal computational modeling work carried out by Noble. Early on, it was also recognized that the interplay between intracellular and surface membrane oscillators, modulated by second messenger pathways, was likely to be important in the overall regulation of cardiac pacemaking (for example, see Berridge and Rapp for an interesting discussion of a variety of coupled oscillators including the pacemaker) and a prominent contribution of $\text{Ca}^{2+}$ cycling was implicated. In the 1990s, the biophysical properties of ion channels with special properties (eg, $I_{\text{KAC}}$ and $I_f$) and a sinoatrial nodal distribution were characterized in detail at the single channel level and cloned, and this discovery work continued after the turn of the millennium, most recently with the description of TRP channels in the atria. In parallel studies over the past 30 years, much of the focus has been on what controls the rate of spontaneous pacemaking in single nodal cells, yet equally important advancements were being made to elucidate how the earliest sites of P-wave activation shift from one site to another during changes in autonomic tone. In this scenario, changes in rate could be manifested by changes in the location of the dominant pacemaker rather than simply by rate modulation in one group of nodal cells.

In the coming months in this thematic review series, we will delve into some of the outstanding issues and controversies at the forefront of scientific investigation into cardiac pacemakers, beginning with the latest ideas about the molecular signals that determine pacemaker development, the controversies surrounding the relative contributions of key scientists.
intracellular (eg, SR Ca\(^{2+}\) cycling) versus sarcolemmal components of membrane potential oscillation, and what insights can, or cannot, be drawn from optical mapping studies of the nodal pacemaker regions. Finally, our guest editor, Dr Denis Noble will provide an overview of the series, including an historical perspective along with outstanding questions to be addressed in future investigations.

In this issue of Circulation Research, the series begins with a review of the mechanisms underlying pacemaker development, an interesting story of the unique role of localized suppression of working muscle differentiation by transcriptional repressors. Enjoy the series and rest easy, nature has taken care of everything.

**Disclosures**

None.

**References**


**Key Words:** pacemaker • sinoatrial node • conduction system • electrophysiology • Ca\(^{2+}\) oscillation
Be Still, My Beating Heart: Never!
Brian O'Rourke

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