

## Modeling pacemaker deterioration with age

Caitlin Sedwick

New JGP study models how sinoatrial node pacemaker activity changes in aged hearts.

Heartbeat pacing is coordinated by a lump of specialized heart muscle tissue called the sinoatrial node (SAN), which integrates inputs from the nervous system with its own intrinsic pacemaking activity to meet the body's metabolic demands. SAN function deteriorates in elderly people, in ways that remain poorly understood. A paper by Joachim Behar and Yael Yaniv, published this month in JGP, uses mathematical modeling to examine how SAN function deteriorates with age and how it can be restored (1).

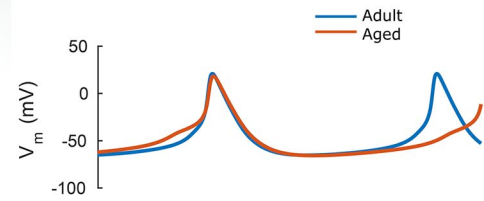
At its root, a SAN cell's pacemaker activity is expressed as rhythmic action potentials driven by the activity of two plasma membrane proteins—the so-called “funny channels” and the sodium/calcium exchange pump (NCX)—that work to bring the membrane voltage to levels that will eventually trigger an action potential. These two proteins are therefore very important to SAN pacemaking.

SAN pacemaking activity also involves the sarcoplasmic reticulum (SR), which undergoes rhythmic local calcium ( $\text{Ca}^{2+}$ ) release events that can trigger plasma membrane action potentials by activating NCX.  $\text{Ca}^{2+}$  also activates adenylyl cyclases that convert ATP to cyclic AMP (cAMP) and activate the kinase PKA. cAMP binds to and enhances activity of funny channels (particularly HCN4), whereas PKA indirectly activates SERCA, a pump that returns  $\text{Ca}^{2+}$  to the SR to allow for subsequent local  $\text{Ca}^{2+}$  release events. Finally, signaling from the autonomic nervous system can modulate both plasma membrane and SR pacemaking activity. For example, signaling by  $\beta$ -adrenergic receptors accelerates heartbeat by generating cAMP and activating PKA through adenylyl cyclases. Clearly, there is a high degree of interconnectedness in this system.

“With a mathematical model you can get a lot of insight into what is going on by changing one mechanism and seeing how the others change in response,”



Authors Joachim Behar (left) and Yael Yaniv (right) used a mathematical model to explore how pacemaker activity in aged cells differs from and can be restored to that in younger adults (simulated pacemaker traces are shown in the graph at right). PHOTOS COURTESY OF THE AUTHORS.



explains Yaniv, an assistant professor at Technion-IIT in Haifa, Israel. To explore how SAN function deteriorates in aged cells, Behar and Yaniv based their model on an earlier one that takes into account both plasma membrane and SR pacemaker activity (2, 3). The new model additionally incorporated nervous system inputs and integrated in vivo observations about how SAN function changes in aged mice (4, 5).

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Prior studies indicated that aged SAN cells have reduced funny channel currents and impaired SERCA and SR  $\text{Ca}^{2+}$  channel activity. When Behar and Yaniv incorporated these factors into their new model, they observed that simulated SAN pacemaker activity slowed down, just as it does in actual aged cells (6). The model also demonstrated how changes to these parameters affected the function of other SAN proteins: for example, by causing decreased currents from plasma membrane ion channels and from NCX in aged cells.

How do aged SAN cells' internal clocks respond to inputs from the autonomic nervous system? The authors simulated the effects of drugs (isoproterenol and IBMX) that elevate cAMP levels and increase PKA activity. Earlier studies indicated that adult

and aged mice have identical maximal heart rates in response to these drugs, but curiously, the simulated aged maximal pacemaker rate was slower than adults'.

“When the model didn't work we started looking at what else could be different about aged cells,” recalls Yaniv. She wondered whether the mismatch could arise because aged SAN pacemaker elements, such as the funny channel or SERCA, have different sensitivity to the effects of cAMP or PKA, respectively. Indeed, adjusting these parameters restored the maximal pacemaker rates of simulated aged cells.

The fact that the processes that drive SAN pacemaker function are so interconnected means it should be possible to target some components of the system to relieve functional deficits in others, even if the targeted protein is not the one malfunctioning. Leveraging this, the authors' model predicts drug doses and genetic interventions that may help treat clinical SAN deterioration—something that Behar and Yaniv plan to investigate next.

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csedwick@gmail.com

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