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EDITORIAL COMMENT

The Tell-Tale Heart (Now, Optically Mapped)*

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In Edgar Allan Poe's short story (1) published in 1843, a nameless narrator murders an old man, dismembers the body, and then hides it under the floorboards. When the police come to investigate, the murderer becomes quickly tormented by what he perceives is the sound of the dead man's heartbeat and compels the officers to tear up the floorboards. As with the narrator in Poe's classic work of fiction, countless researchers over the last century have been compelled to seek out the source of the heartbeat.

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The sinoatrial node (SAN) has similarly obsessed anatomists, physiologists, and cardiologists for more than 100 years since its original description by Keith and Flack in 1907 (2). The fascination spans the spectrum from the molecular origins of pacemaker automaticity to the anatomic and physiologic mechanisms of macroscopic propagation of the sinus node impulse to neighboring atrial tissue. At all levels, fascination has been accompanied by controversy. Even 1 of the discoverers of the SAN is controversial, Sir Arthur Keith being allegedly involved (3) in the scientific scandal involving the fabrication of "piltdown man," an evolutionary missing link. Recently, Circulation Research published a series of articles reviewing and revitalizing controversies around the SAN (4–8). The molecular mechanisms of pacemaker activity generation have been disputed between several proposed mechanisms, including various inward membrane currents (I_f, T- and L-type Ca^{2+} currents, the "membrane voltage clocks") as well as intracellular Ca^{2+} cycling (the "calcium clocks" (7,9,10), involving release from the sarcoplasmic reticulum and possibly store-operated Ca^{2+} channels [11]). Details of the generation of the pacemaker activity can be found elsewhere (7).

Just as interesting, however, are the mechanisms of impulse conduction from the SAN to the atria at the macroscopic level. Successful propagation from the central pacemaker cell (or group of cells) to atrial tissue is a tremendous physiological challenge. Normal propagation in cardiac tissue entails a delicate balance between depolarized cells (source) and the resting tissue ahead (sink) (12). Excited cells serve as a source of electric charge for depolarizing neighboring cells (sink). The relationship between source and sink defines the safety factor of propagation. A large volume of excited tissue (source) will easily propagate into a small volume of quiescent tissue (sink). Alternatively, if the sink is too large, propagation fails due to a source–sink mismatch. How does the SAN manage to take depolarization from a small group of cells into the entire atrial tissue? Cellular coupling holds the key to this challenge. In conduction failure due to source–sink mismatch, propagation fails because cells close to the wave front fail to depolarize as the neighboring, well-coupled unexcited tissue downstream holds their membrane potential polarized. It is known that propagation from a small group of cells (source) into a large group of well-coupled cells (sink) has a low safety factor and is likely to fail. In this scenario, decreasing cellular coupling—e.g., via decreasing gap junction conductance—can paradoxically enhance propagation success, despite slowing conduction velocity (13). It is intuitive that a similar mechanism must play a role in propagating SAN conduction. The slow conduction within the SAN supports uncoupling as a mechanism of slow-but-safe propagation. How to successfully conduct from SAN to sites of initial atrial activation remains challenging to explain.

Mapping studies (14,15) have shown that initial atrial activation sites can vary widely during sinus rhythm. In their 1914 study, Meek and Eyster (15) used multiple string galvanometers and, by identifying locations with initial electrical negativity under conditions of vagal stimulation or localized cooling, observed that initial atrial activation sites can vary. In 1978, Boineau et al. (16) observed a trifocal origin of the atrial waveform in the dog using multiple bipolar atrial electrode recordings. The subsequent Boineau-Schuessler SAN model proposed the existence of discrete conduction pathways connecting the SAN with atrial tissue to explain beat-to-beat divergent activation sites (16–18).

In this issue of the *Journal*, Fedorov et al. (19) add to the authors' extensive contribution over many years to the study of the SAN. In particular, the development of the technique of optical mapping has provided a modality by which to study the relationship between SAN anatomy and physiology to begin to explain SAN function. Applying this technique, they recently found evidence for discrete exit pathways connecting the SAN and atria in the dog (20). They were able to directly map the conduction inside the canine SAN and atrium, and identified 2 or more discrete conduction pathways directed superiorly or inferiorly from

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the SAN. Interestingly, they measured slowing of conduction velocity in these pathways down to 2 cm/s, and attributed this to source–sink mismatch. They concluded that the etiology of multifocal atrial activation is due to the possibility of atrial excitation from any of multiple discrete SAN exit pathways. In the current report, they have extended these findings to the human, for the first time applying optical mapping techniques to obtain voltage recordings of the coronary perfused intact human SAN and nearby atria during normal sinus rhythm. They confirm the human SAN is electrically insulated from nearby atrial myocardium with the exception of several discrete exit pathways, noting a similar slowing of conduction within these pathways as in the canine study. From the source–sink mismatch point of view, this insulation makes sense and seems necessary: if the atrial tissue were well coupled to the pacemaker cells, propagation within the SAN would fail due to excessive current sink.

Controversies remain in the interpretation of the optical action potential signals (which are a superposition of signals from overlapping atrial myocardium and SAN layers) as well as in the role of calcium dynamics in pacemaker activity (5). Notwithstanding such, understanding the mechanism that overcomes the source–sink mismatch is likely to have important clinical implications. The authors suggest that decreased conduction velocity is a result of the mismatch; another explanation may be that cell–cell coupling is reduced in these exit pathways so as to increase the safety factor for propagation, i.e., to overcome the source–sink mismatch. These questions and more remain; however, the current report continues a fruitful tradition of comparative physiology research going back over 100 years, and thanks to this work, we are no doubt closer to solving the controversies than ever before.

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Key Words: bradycardia ■ exit pathway ■ optical mapping ■ sinus node.