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ARRHYTHMIAS

Safety backups to keep the pace

> Total cardiac arrest occurs only when all pacemakers or conduction pathways fail

The human sinoatrial node (SAN), the main pacemaker of the heart, has redundant, fail-safe mechanisms that maintain a consistent heart rhythm and protect the heart from rhythm failure even under stress conditions, according to a new study published in *Science Translational Medicine*. "[We found that] the human SAN is hardwired with a backup system, with three diverse regions of pacemakers acting as batteries and up to five conduction pathways that act as wires to connect the signal to the atria," explains Vadim Fedorov, lead investigator of the study.

The presence of multiple intranodal pacemakers and several sinoatrial conduction pathways (SACPs) in the human SAN complex was proposed more than 30 years ago, but the functional, structural, and molecular characteristics underlying the robustness of this complex remained untested. "Studying the human SAN pacemaker complex has been challenging, as it is a heterogeneous 3D structure that lies within the atrial wall, and clinical electrode recordings are limited to only surface atrial activation," notes Fedorov. "Furthermore, the human SAN differs greatly from well-studied experimental animal models," he adds. To overcome these issues, Fedorov and colleagues used explanted human hearts and integrated high-resolution, near-infrared optical mapping — which allows 3D visualization of the spontaneous electrical activity within the SAN complex — with 3D histology reconstruction and molecular mapping to study the function of the different SAN pacemakers and conduction pathways.

The *ex vivo* coronary-perfused hearts had a stable intrinsic sinus rhythm similar to the rates measured *in vivo*. To study SAN function under stress conditions, the investigators challenged the hearts with adenosine, a regulator of sinus rhythm that is overproduced in heart failure or in ischaemic conditions. During the adenosine challenge, the primary central pacemaker in the SAN was suppressed, but the superior and inferior intranodal pacemakers (which were previously inactive) were able to maintain automaticity. In addition, when the preferential SACP was suppressed, other SACPs rescued sinus rhythm by delivering electrical impulses to the atria. These findings suggest the presence of two independent fail-safe mechanisms for automaticity and conduction. "Total cardiac arrest occurs only when all pacemakers or conduction pathways fail," points out Fedorov.

Mechanistically, the investigators showed that the heterogeneous distribution of adenosine receptor A_1 and G-protein-activated inward rectifier potassium channel 4 protein expression across the SAN complex regulates the fail-safe mechanism in response to adenosine challenge.

To support the clinical translational application of their observations, the research team validated their results using electrocardiogram and clinically-used bipolar catheters to record atrial and SAN activity simultaneously in the explanted hearts. "[This measurement] is the first step in diagnosing intranodal mechanisms underlying SAN dysfunction with clinically-available techniques," says Fedorov. "Our next quest is to work with electrophysiologists to identify more precisely who needs a pacemaker implant and who still has backups and can get along without one."

Stanley Nattel, from the Montreal Heart Institute in Canada, who was not involved in the study, points out that addressing SAN complex anatomy with the improved mapping methods used in this study was needed. "Phenomena that had been described or suggested before were confirmed in an elegant fashion," remarks Nattel, and explains that another important contribution is that the sites of pacemaker shift under adenosine were shown to express lower levels of the adenosine receptor A_1 compared with the dominant SAN pacemaker. "The next step might be to examine the determinants of SAN pacemaker shifts under other, physiologically-relevant paradigms, for example, high cholinergic tone, knock out or knock down of key SAN pacing determinants like HCN channels or components of the calcium clock, or sinus node ischaemia," proposes Nattel.

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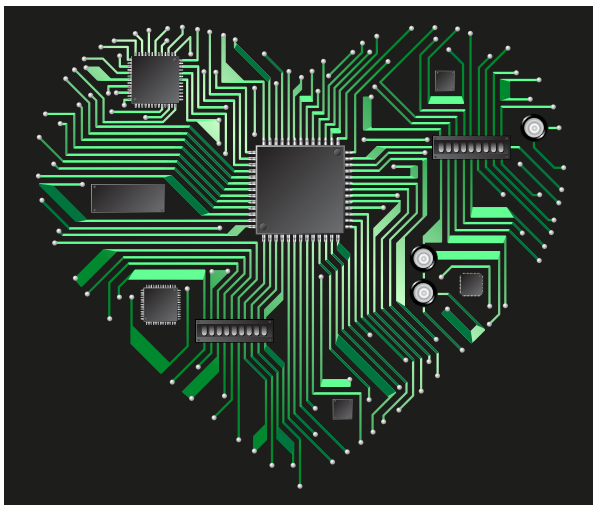

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