

# Letter to the Editor

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## The Sinoatrial Node: Cell Size Does Matter

To the Editor:

The key point of the recently published report in *Circulation Research*<sup>1</sup> by Lyashkov et al is that action potential characteristics (including beating rate) and  $\text{Ca}^{2+}$  handling are independent of the size of the sinoatrial node (SAN) cell in the rabbit. This is an allusion to our work; since 1996, in a series of 8 articles, we have reported that action potential characteristics (including beating rate), density of ionic currents,  $\text{Ca}^{2+}$  handling, and density of connexins are dependent on the size of the SAN cell in the rabbit.<sup>2-9</sup> How can this discrepancy be explained?

From the leading pacemaker site in the SAN center in the intercaval region (between superior and inferior vena cava), the action potential propagates to the SAN periphery on the endocardial surface of the crista terminalis. The furthest extent of the SAN is the right branch of the sinoatrial ring bundle (RSARB), a vestige of the embryonic venous valve, on the crest of the crista terminalis. To study regional differences in electrical activity, we have cut a strip of tissue from the center to the periphery (intercaval region to RSARB) and tied it into a series of  $\approx 0.25$ -mm balls by ligatures.<sup>10</sup> The balls are labeled A to D, etc, and ball A is always from the periphery and includes the RSARB. All balls show spontaneous activity (being SAN), but there are characteristic differences between them; eg, in ball A from the periphery, the beating rate is faster and the maximum upstroke velocity of the action potential ( $dV/dt_{\max}$ ) is higher ( $dV/dt_{\max}$  is  $\approx 50$  V/sec in ball A, but  $<10$  V/sec in central balls).<sup>10,11</sup> The same differences in electrical activity (except beating rate of course) are observed in the intact SAN.<sup>10</sup> The action potential upstroke is sensitive to  $\text{Na}^+$  current ( $I_{\text{Na}}$ ) block by tetrodotoxin in ball A from the periphery but not in the central balls, suggesting that the upstroke is  $I_{\text{Na}}$  dependent in the periphery but not the center.<sup>11</sup> Recently, we have shown the molecular basis of this: the  $\text{Na}^+$  channel,  $\text{Na}_v1.5$ , is abundant in the atrial muscle, present in the periphery (especially in RSARB), but absent in the center.<sup>12</sup> In both the center and periphery, there are cells of various sizes, but on average, central cells are smaller than peripheral cells ( $\approx 51$  and  $\approx 88$   $\mu\text{m}$ , respectively, in length).<sup>13</sup> Routinely, we have isolated cells from the whole of the SAN: we cut strips of tissue from the center to the periphery (intercaval region to RSARB) and isolate cells from the strips. We observe characteristic differences in electrical activity: that of small cells is characteristic of the center, whereas that of large cells is characteristic of the periphery; eg, in large cells, the beating rate is faster and  $dV/dt_{\max}$  is higher ( $dV/dt_{\max}$  is  $\approx 50$  V/sec in large cells, but  $<10$  V/sec in small cells).<sup>2</sup> Consistent with this and the electrophysiology of the center and periphery as well as the distribution of  $\text{Na}_v1.5$ , there is only substantial  $I_{\text{Na}}$  in large cells.<sup>2</sup> We have observed other correlations between the characteristics of small and large cells and what is known about the center and periphery, eg, in relation to connexin expression.<sup>7,14</sup> Furthermore, similar correlations between electrophysiological properties and cell size have been observed at the rabbit atrioventricular node.<sup>15</sup>

How can the discrepancy be explained? There is a possibility that real peripheral SAN cells from close to the RSARB were not

included in the cells analyzed by Lyashkov et al.<sup>1</sup> This is supported by the fact that all of their SAN cells have the characteristics of central cells in terms of low  $dV/dt_{\max}$  ( $8 \pm 0.02$  V/s) and lack expression of connexin43. If this were the case, it would not be surprising that Lyashkov et al<sup>1</sup> did not observe cell size dependence of the cellular functional properties of SAN cells.

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## Disclosures

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