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## Cross talk between renal and cardiac autonomic nerves: Is this how renal denervation works?

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### Keywords

stellate ganglion; renal nerve; sympathetic system; renal artery ablation; autonomic nervous system

### Editorial Comment

Surgical renal sympathetic denervation (RSD) has been used to control resistant hypertension.<sup>1</sup> With the development of catheter based RSD, this old technique has been resuscitated for the treatment of hypertension. While initial clinical studies showed effective hypertension control,<sup>2</sup> a recent sham-controlled randomized clinical trial failed to confirm its antihypertensive efficacy.<sup>3</sup> These negative studies notwithstanding, RSD has been actively pursued as a tool to control various types of cardiac arrhythmias.<sup>4,5</sup> The mechanisms by which RSD helps arrhythmia control remain poorly understood. In the present issue of the *Journal*, Huang et al<sup>6</sup> reported in anesthetized dogs that left renal nerve stimulation facilitates ischemia induced ventricular arrhythmia by increasing the function of the left stellate ganglion (LSG). LSG ablation attenuated these arrhythmias. This report suggests that there is a direct interaction between the left renal sympathetic nerve and the LSG. Is it possible that the cross talk between these two nerve structures underlies the antiarrhythmic mechanisms of RSD?

### Left Stellate Ganglion and Cardiac Arrhythmia

LSG nerve activity is a direct trigger of cardiac arrhythmias.<sup>7–9</sup> Left cardiac sympathetic denervation (LCSD) is effective in managing patients with long-QT syndrome and catecholaminergic polymorphic ventricular tachycardia.<sup>10–12</sup> In addition to genetic arrhythmias, both LCSD and bilateral cardiac sympathetic denervation may be effective in controlling ventricular tachycardia (VT) storm or refractory VT.<sup>13</sup> These studies indicate that LSG is an important arrhythmogenic structure.

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## RSD and Cardiac Sympathetic Nerve Activity

Various neuromodulation methods have been tested for cardiac arrhythmia control.<sup>14</sup> Among them, low-level tragus stimulation<sup>15</sup> reduces ganglionated plexi neural activity while low level vagal nerve stimulation inhibits both ganglionated plexi and stellate ganglion nerve activities.<sup>16, 17</sup> Stimulating the cardiac sympathetic nerves may cause reflex renal sympathetic nerve activity in dogs.<sup>18</sup> Renal nerve stimulation may significantly alter the renal and cardiovascular function and contribute to the initiation, development and maintenance of hypertension.<sup>19</sup> Li et al<sup>20</sup> demonstrated that RSD reduces BP by partially inhibiting sympathetic drive and systemic sympathetic outflow in hypertensive canine models. In obese spontaneously hypertensive rats, renal sympathetic activation increases while RSD decreases BP, renal injury and cardiac remodeling.<sup>21</sup> In SYMPPLICITY-HTN1 trial, RSD reduced renal noradrenaline spillover 47% in patients with refractory hypertension.<sup>2</sup> Muscle sympathetic nerve activity in patients with resistant hypertension can be substantially and rapidly reduced by RSD.<sup>22</sup> Huang et al<sup>6</sup> extended these observations by demonstrating that left renal nerve stimulation facilitates ischemia induced ventricular arrhythmia by increasing the function of the left stellate ganglion (LSG). They also demonstrated increased nerve growth factor (NGF) in the LSG after left renal nerve stimulation. While the authors did not perform immunohistochemical studies of the heart, a previous study<sup>23</sup> showed that NGF infusion to the LSG can cause cardiac nerve sprouting and sympathetic hyperinnervation. An implication of the present study is that hyperactive renal sympathetic nerves may induce LSG remodeling and increase sympathetic tone, which facilitates the development of arrhythmias.<sup>23, 24</sup> Therefore, ablation of either the renal sympathetic nerve or the LSG may be effective in cardiac arrhythmia control. Consistent with this hypothesis, we<sup>25</sup> have recently found that in ambulatory dogs that RSD is associated with reduced LSG nerve activity and atrial tachycardia episodes.

In summary, LSG plays an important role in cardiac arrhythmogenesis, and that modulating the stellate ganglion nerve activity by RSD may be effective in arrhythmia control. Huang et al<sup>6</sup> provided important information on the interaction between renal sympathetic nerve and LSG. It is therefore possible that the RSD achieves arrhythmia control through the reduction of the stellate ganglion activity and cardiac nerve sprouting. More studies in ambulatory animals and in humans are needed to test the latter hypotheses.

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