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EDITORIAL COMMENT

Vagal Neuromodulation for Atrial Arrhythmias*

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Atrial arrhythmias following cardiac surgery is a well-recognized problem that prolongs hospitalization and increases health care expenses. Post-operative atrial fibrillation (POAF) reflects the dynamic interplay between the underlying cardiac electrical substrate and its modulation by the cardiac nervous system, both of which can be altered by the surgical procedures, especially by local reactive inflammatory processes (1). Standard care using antiarrhythmic pharmacological therapy for POAF has had limited efficacy (2). Autonomic regulation therapy is an emerging therapeutic option that leverages control of autonomic activities to impact organ function, in this case the heart.

Autonomic control of the heart reflects the delicate interplay between intrathoracic, spinal cord, brainstem, and higher center reflexes (3,4). Intrathoracic reflexes comprise the intrinsic cardiac and intrathoracic (stellate/middle cervical/mediastinal) ganglia and are primarily associated with cardiocentric control on a beat-to-beat basis (3,4). Central reflexes involve sensory inputs conveyed by nodose, dorsal root, and petrosal ganglia to various regions of the central nervous system (spinal cord, nucleus of the solitary tract, hypothalamus, and so forth) with primary control of whole-body homeostasis (3,4). Imbalances within and between these layers of reflex neural control, either inherent or acquired, can be arrhythmogenic and therefore can also serve as targets for bioelectronic modulation.

SEE PAGE 929

The paper by Stavrakis et al. (5) in this issue of *JACC: Clinical Electrophysiology* evaluates the effects of low-level vagus nerve stimulation (VNS), applied extrapericardially but just rostral to the heart, where the intrathoracic vagosympathetic trunk runs between the superior vena cava and ascending aorta. Patients undergoing cardiac surgery, including coronary artery bypass graft and/or value surgery, were selected for this study. In a randomized design, half of the patients received VNS at a level that was 50% of the bradycardiac threshold as determine at 20 Hz and 0.1-ms duration and maintained until discharge from the intensive care unit (~61 h of treatment). The remaining patients had electrode implant but with no stimulation. The authors reported a significant drop in POAF in the treatment group (12% vs. 36%) and a corresponding decrease in serum levels of tumor necrosis factor-α and interleukin-6. The data are consistent with the conclusions that low-level VNS can reduce the arrhythmia potential and mitigate inflammation.

Bioelectronic neuromodulation engages various levels of autonomic control, depending on the characteristics of stimulation and the site to which it is applied. The site leveraged in the Stavrakis et al. (5) study is a location where there are mixed nerves containing afferent (thoracic and visceral) and efferent (parasympathetic and sympathetic) projections (6). The inability of a subset of selected patients to respond to even the highest intensity levels of nerve stimulation may reflect the fact that many of the parasympathetic efferent projections to atrial tissues may

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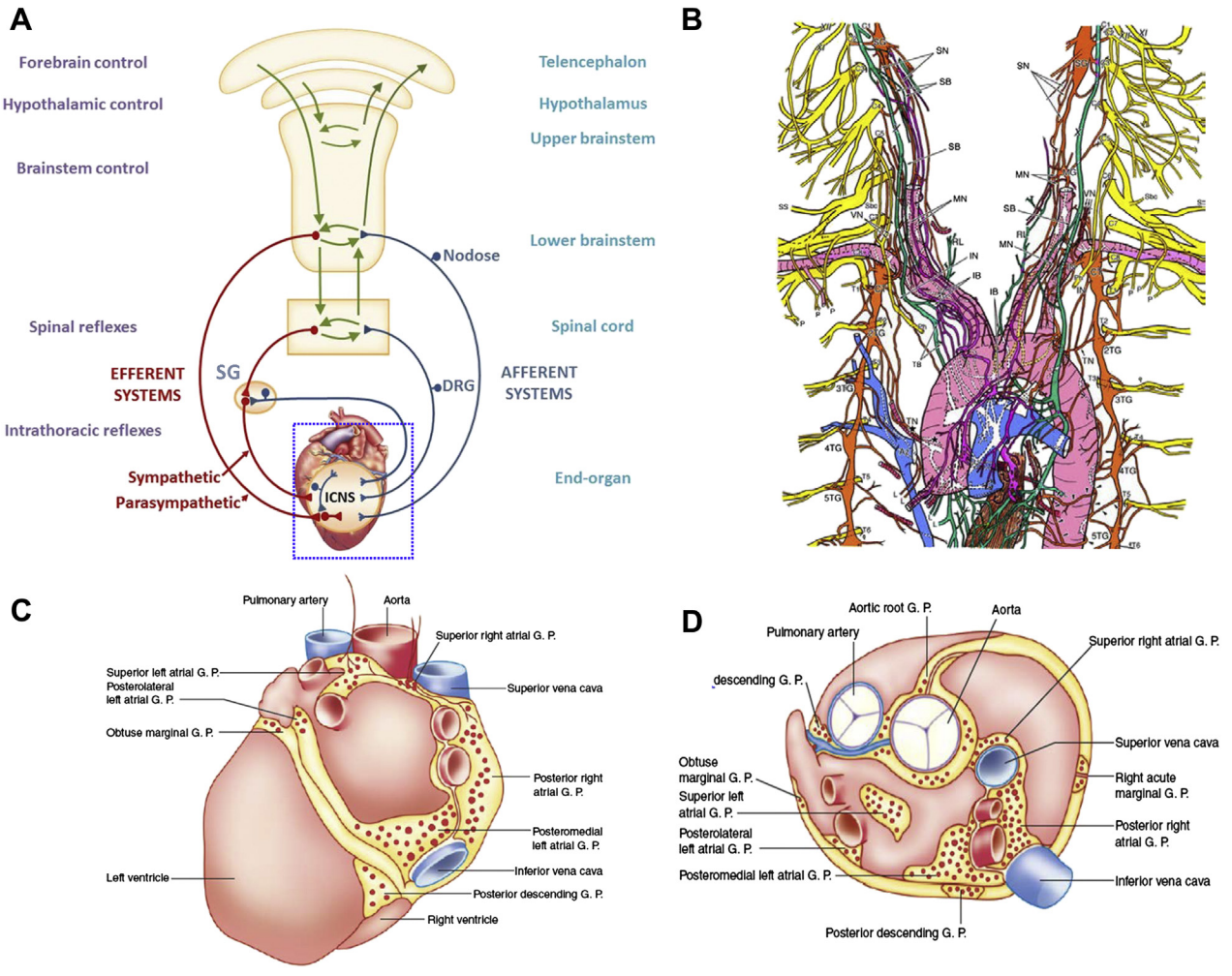
All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

FIGURE 1 Human Cardiac Neuroanatomy



(A) Functional organization of cardiac innervation. **(B)** Diagram of the origin, course, and distribution of the autonomic cardiac nerves viewed from a ventral aspect (Adapted with permission from Kawashima [8]). The sympathetic cardiac nerves, vagal cardiac branches, and the mixture nerves (cardiac plexus) are colored in **orange**, **green**, and **purple**, respectively. **(C and D)** Ganglionated plexi of the human heart (Modified with permission from Armour et al. [11]). The images show the aggregation of neurons on the surface of the heart in the various named ganglionated plexi in epicardial fat pads. AI = anterior interventricular branch; Ao = aorta; Az = azygos vein; CB = circumflex branch; CC = common carotid artery; CT = cervicothoracic (stellate) ganglion; DRG = dorsal root ganglion; GP = ganglionated plexi; GV = great cardiac vein; IB = inferior (vagal) cardiac branch; ICNS = intrinsic cardiac nervous system; IG = inferior cervical ganglion; IN = inferior cervical cardiac nerve; L = lung; LA = left atrium; LCA = left coronary artery; MG = middle cervical ganglion; MN = middle cardiac nerve; P = pectoral nerve; Ph = phrenic nerve; PT = pulmonary trunk; RA = right atrium; RCA = right coronary artery; RL = recurrent laryngeal nerve of vagus nerve; SB = superior (vagal) cardiac branch; Sbc = nerve to subclavian muscle; SG = superior cervical ganglion; SN = superior cardiac nerve; SS = suprascapular nerve; SVC = superior vena cava; TB = thoracic (vagal) cardiac branch; TG = thoracic ganglia; TN = thoracic cardiac nerve; VG = vertebral ganglion; VN = vertebral nerve; X = vagus nerve; XI = accessory nerve; XII = hypoglossal nerve.

have exited the vagosympathetic trunk rostral to the chosen stimulation site (7,8), the selection of a pulse width of 100 μs (9), and/or opposing effects on parasympathetic activity evoked from afferent versus efferent axon activation (9,10). It should also be recognized that the area being stimulated is anatomically close to the posterior atrial ganglionic plexus (11), a region that regulates major sympathetic-parasympathetic interactions for control of atrial function (12,13) (**Figure 1**). As appropriately pointed by Stravakis et al. (5), although effective in this implementation for POAF control neither the stimulation site for VNS nor the stimulation protocols have been optimized. It is also likely that stimulation protocol optimization for 1 target effect (e.g., POAF) is different from another target (e.g., anti-inflammatory influences).

Memory function as it relates to VNS, both for POAF and the anti-inflammatory effects, is another important aspect brought forth in the Stravakis et al. (5) study. For POAF, even though VNS was only maintained for ~61 h, the efficacy against atrial fibrillation was maintained throughout the 1-month follow-up period. With regards to the antiarrhythmic effects to short-duration (3 min) VNS for atrial fibrillation, that effect lasts for ~26 min (14). The memory function to more prolonged VNS may be correspondingly greater. Alternatively, it should also be considered that major changes in intrinsic cardiac network excitability occur within the first 4 days after a major cardiac perturbation (15) and the presence of VNS may downregulate excitability in this critical time of remodeling (16) to help maintain atrial electrical stability. The anti-inflammatory effects associated with VNS reported in are consistent with previous data (17) and it is remarkable that even short-duration VNS daily can exert long-lived influences. This memory function can have important implications for clinical implementation of multiple forms of autonomic regulation therapy (3,4).

Understanding the dynamics between neurohumoral control mechanisms of the heart in health and the adaptation to stress can provide new clues for treatment. Some of these stresses, such as ischemia, can be catastrophic (18,19); other types produce slower transitions to compromised cardiac function (20,21). With increased understanding of the structure/function organization for cardiac control, bioelectronic approaches and neuropharmacological approaches can be applied to manage these problems (22,23). Eventually "closed-loop" modes of treatment can be developed to help preserve cardiac electrical and mechanical function, even in the setting of structural heart disease.

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