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ANATOMY CARD: DA VINCI CORNER

Anatomy and Physiology of Intrinsic Cardiac Autonomic Nervous System

Da Vinci Anatomy Card #2

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INTRODUCTION

Following demonstration that the intrinsic cardiac nervous system (ICNS) is a potential modulator of the initiation and perpetuation of atrial fibrillation and the major reason for several bradyarrhythmias, catheter-based autonomic modulation emerged as a novel therapy in recent years (1,2). The anatomy and physiology of the ICNS are relevant to the cardiac electrophysiologist because this invisible anatomic structure is becoming an important target during radiofrequency catheter ablation.

PRINCIPLES OF AUTONOMIC INNERVATION OF THE HEART

Autonomic innervation of the heart may be divided into the extrinsic (central) cardiac nervous system and the ICNS. By definition, a ganglion is a cluster of neuron cell bodies in the peripheral nervous system. The extrinsic part consists of the nuclei in the brain stem and along the thoracic segments of the spinal cord, as well as their axons en route to the heart. Preganglionic sympathetic axons arise from the spinal cord, synapse with the second sympathetic neurons in the sympathetic chain or intrinsic cardiac ganglia, and proceed as the post-ganglionic sympathetic axons innervating the cardiomyocytes. Preganglionic parasympathetic axons of the vagus nerve primarily arise from the dorsal vagus nerve and possibly the nucleus ambiguus and synapse with the second parasympathetic neurons within epicardial ganglionated nerve plexuses.

MICROANATOMY OF THE INTRINSIC CARDIAC NERVOUS SYSTEM

Most neurons of the ICNS reside inside epicardial ganglia that are interconnected by intrinsic nerves on the human atria and ventricles (**Figure 1**) (3). Earlier reports suggested that only the second parasympathetic neurons exist in the ganglia. However, according to more recently published reports, these ganglia contain both efferent parasympathetic and sympathetic neuronal somata and presumably local circuit neurons or interneurons, and these are very densely packed, overlapping, and of widely varying sizes (**Figures 1A to 1E**) (3–5).

SELECTIVE INNERVATION OF THE SINOATRIAL AND THE ATRIOVENTRICULAR NODES

For many years, studies of the hearts of larger mammals (e.g., canine, primate, ovine studies) have mostly focused on determining the location of epicardial ganglia by using histological examination of heart sections, an approach that led to the suggestion of the ganglionated plexuses (GPs) concept consisting of grouping ganglia in different sites (6–8). On the basis of physiological experiments, investigators determined that most GPs are embedded around 3 epicardial fat pads (**Figures 2A and 2B**). Although surgical removal of the epicardial ganglia located at the junction of the inferior vena

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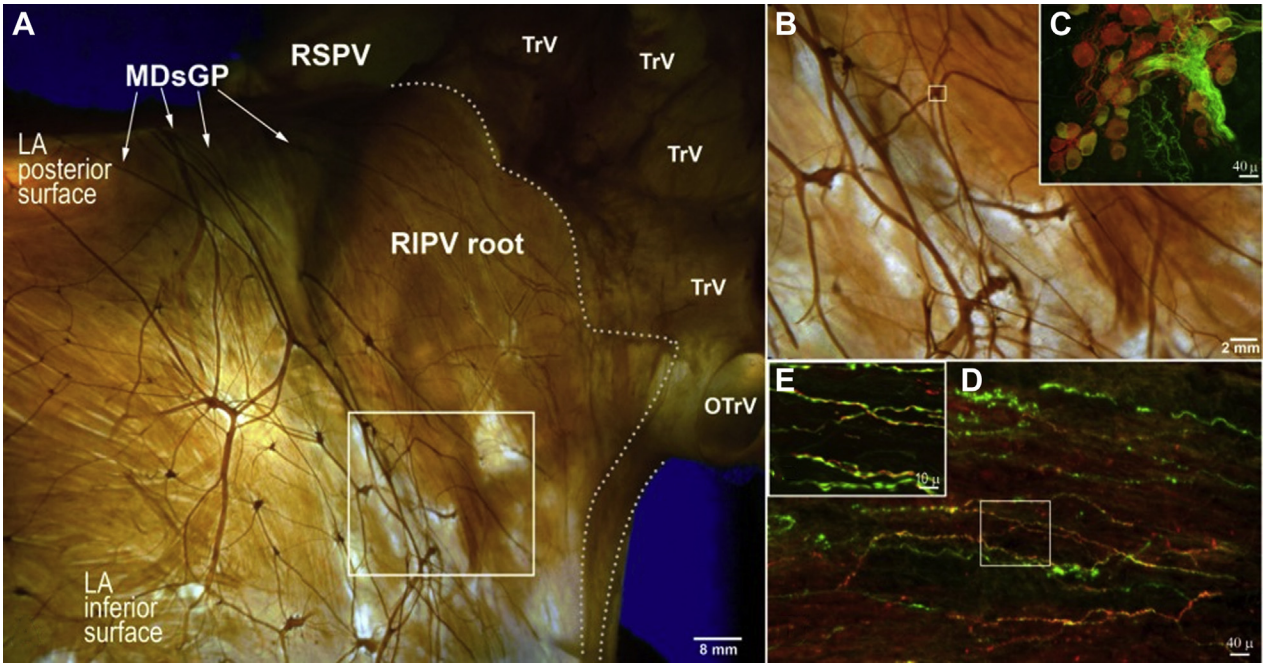
FIGURE 1 Nerve Supply of the Human RIPV by the MDsGP



(A) Macrophotograph of the posteroinferior surface of left atrium (LA) with the right inferior pulmonary vein (RIPV) stained histochemically for acetylcholinesterase. The **dotted line** indicates the reflection of serous pericardium into epicardium (heart hilum limits). Note the course of epicardial ganglionated nerves extending from the middle dorsal ganglionated nerve subplexuses (MDsGP) to the root of the right inferior pulmonary vein. **(B)** The **white frame on A** is enlarged to illustrate the ganglionated nerves from which the nerves proceeding toward the walls of right inferior pulmonary vein originate. **(C)** The **small boxed area in B** is magnified to demonstrate the ganglionic cells stained immunohistochemically for tyrosine hydroxylase **(green)** and for acetyltransferase **(red),** which are reliable neuronal markers for adrenergic and cholinergic intrinsic cardiac neurons, respectively. Note that some neuronal somata are biphenotypic (i.e., they are simultaneously positive for adrenergic and cholinergic neuronal marker). **(D)** Microphotograph of neural meshwork of nerve fibers between cardiac myocytes of the right inferior pulmonary vein. The immunohistochemically stained nerve fibers are positive for both the adrenergic **(green)** and cholinergic **(red)** neuronal markers. **(E)** The **boxed area in D**, in which the paired adrenergic **(green)** and cholinergic **(red)** post-ganglionic axons are clearly visible. OTrV = orifice of the tributary vein of the right inferior pulmonary vein; RSPV = right inferior pulmonary vein; TrV = roots of the tributary veins.

cava and inferior wall of the left atrium selectively eliminated the negative dromotropic effects of vagal nerve stimulation, surgical removal of the epicardial ganglia located around the right pulmonary veins attenuated the negative chronotropic response to vagal nerve stimulation without adversely affecting vagal inhibition of atrioventricular conduction (**Figures 2C and 2D**) (6,7).

ORGANIZATION OF THE INTRINSIC CARDIAC AUTONOMIC NERVOUS SYSTEM IN HUMANS

A similar GP-based terminology was proposed for humans by Armour et al. (9). The following 5 major and 1 minor atrial locations were consistently identified and called GPs: the superior right atrial GP, the superior left atrial GP, the posterior right atrial GP, the posteromedial left atrial GP, the interatrial septal GP, and the posterolateral left atrial GP. However, the exact number of these ganglia was identified later by Pauza et al. (3), who counted these ganglia on whole heart preparations (nonsectioned). This finding suggested that the number of ganglia in the human heart varies from heart to heart and ranges from 706 up to 1,560. Furthermore, staining of the intrinsic cardiac neural plexus on the whole human heart demonstrated that the heart is under neuronal control through 1 intrinsic epicardiac neural plexus, from which nerves extend to distinct cardiac regions by following 5 atrial pathways that were named epicardial ganglionated subplexuses (sGP) (**Figures 3A and 3B**): 1) *the ventral right atrial sGP* occupies the following regions: ventral superior right atrial region, the ventral side of the root of the superior vena cava, and the ventral inferior right atrial region; 2) *the ventral left atrial sGP* occupies essentially the ventral

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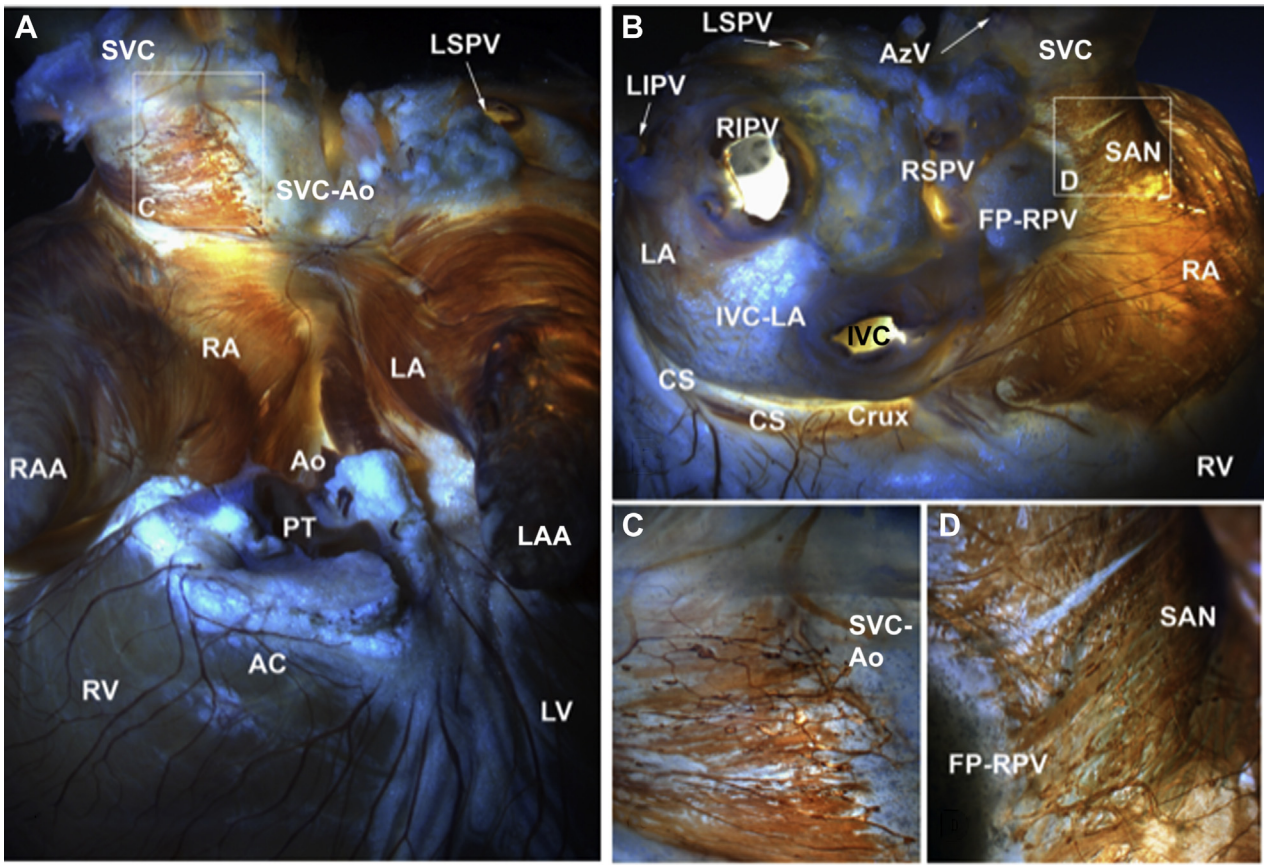
FIGURE 2 **Macrophotographs of Pressure-Inflated Canine Hearts**

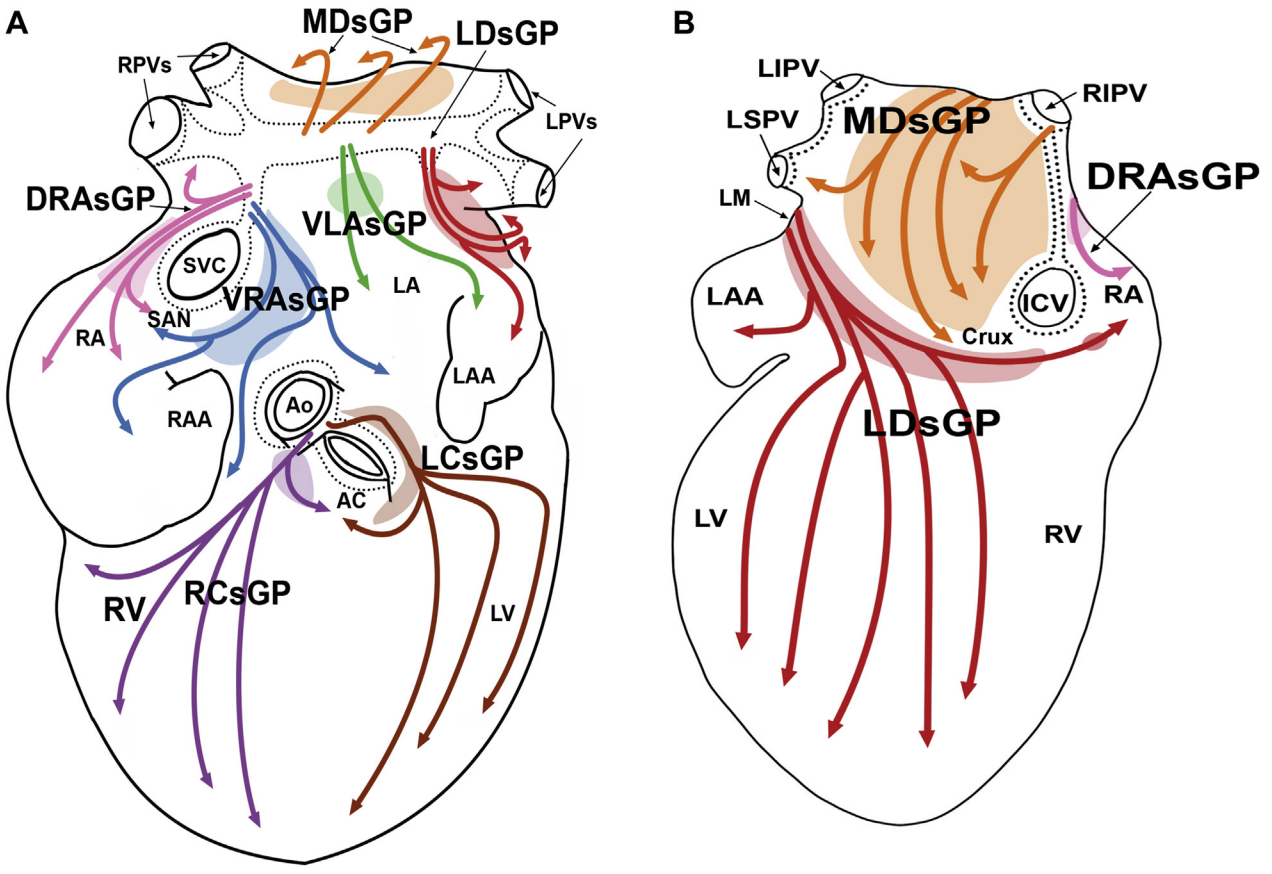


(A) Anterior. **(B)** Posterior. The relationship of the distinctive fat pads (FP) (superior vena cava–aortic [SVC-Ao], right pulmonary veins [FP-RPV], and inferior vena cava–left atrial [IVC-LA]) with the epicardial ganglionated nerves stained histochemically for acetylcholinesterase seen as **dark brown lines** in the epicardium. The **dotted line** indicates the reflection of serious pericardium into epicardium that limits the venous part of heart hilum. **(C) Boxed area in A** enlarged. **(D) Boxed area in B** enlarged. Note the numerous epicardial ganglia that distribute on the root of superior vena cava, including the area of the sinoatrial node (SAN). AC = arterial conus; Ao = root of ascending aorta; AzV = azygos vein; Crux = fossa at the orifice of coronary sinus or "crux cordis"; CS = coronary sinus; LAA = left atrial appendage; LA = left atrium; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; LV = left ventricle; PT = root of pulmonary trunk; RAA = right atrial appendage; RA = right atrium; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein; RV = right ventricle; SVC – superior vena cava.

superior left atrial region; 3) *the left dorsal sGP* distributes across the left coronary sulcus, the region of the dorsal left coronary sulcus, and the middle left atrial region regions and contains abundant ganglia; 4) *the middle dorsal sGP* occupies the dorsal superior left atrial region and around the crux cordis; and 5) *the dorsal right atrial sGP* occupies mainly the dorsal superior right atrial region, the dorsal side of the root of the superior vena cava, and the region over the interatrial septum.

The sympathetic and parasympathetic post-ganglionic axons involving post-ganglionated nerves of the ventral right atrial sGP extend mostly into the ventral atrial regions, and some of these nerves may innervate the sinoatrial node. It is noteworthy that most of the post-ganglionated nerves of this sGP passing onto the left atrium invariably extend through a remarkable crest of the ventral surface of the left atrium. Post-ganglionated nerves from the left dorsal, middle dorsal, ventral right atrial, and dorsal right atrial sGPs extend toward the interatrial septum and presumably supply the atrioventricular nodal region. A 3-dimensional mapping-based representation of distribution of the sGPs is provided in Figure 4.

FIGURE 3 Schematic Drawing of the Location, Course, and Innervation Regions of the 7 Human Epicardiac Subplexuses



(A) Anterosuperior view. **(B)** Posteroinferior view. In spite of a scattering of sparse ganglia on the human ventricles, only the main locations with the highest density of the subplexus ganglia are depicted by shadowing in color that corresponds the specific ganglionated subplexus (sGP) The **dotted lines** indicate the limits of the heart hilum through which nerves access the epicardium. Ganglionated subplexuses are delineated in distinct colors: blue, ventral right atrial ganglionated subplexus (VRAsGP); green, ventral left atrial ganglionated subplexus (VRAsGP); magenta, right coronary ganglionated subplexus (RCsGP); brown, left coronary ganglionated subplexus (LCsGP); red, left dorsal (LDsGP); orange, middle dorsal ganglionated subplexus (MDsGP); and pink, dorsal right atrial ganglionated subplexus (DRAsGP). Note that nerves derived from 3 ganglionated subplexuses (left coronary, middle dorsal, and dorsal right atrial) innervate the human pulmonary veins. LM = ligament of Marshall or nerve fold; LPVs = left pulmonary veins; other abbreviations as in Figure 2.

CONCLUSIONS

Although terminology varies between neuroanatomists and electrophysiologists, the route of innervation to the heart tends to be consistent. The major difference between the previous GP nomenclature and that of sGP is that GPs are actually parts of the larger specific sGPs. A thorough understanding of these anatomic principles of cardiac innervation may help create a framework for modern therapies directly targeting the ICNS.

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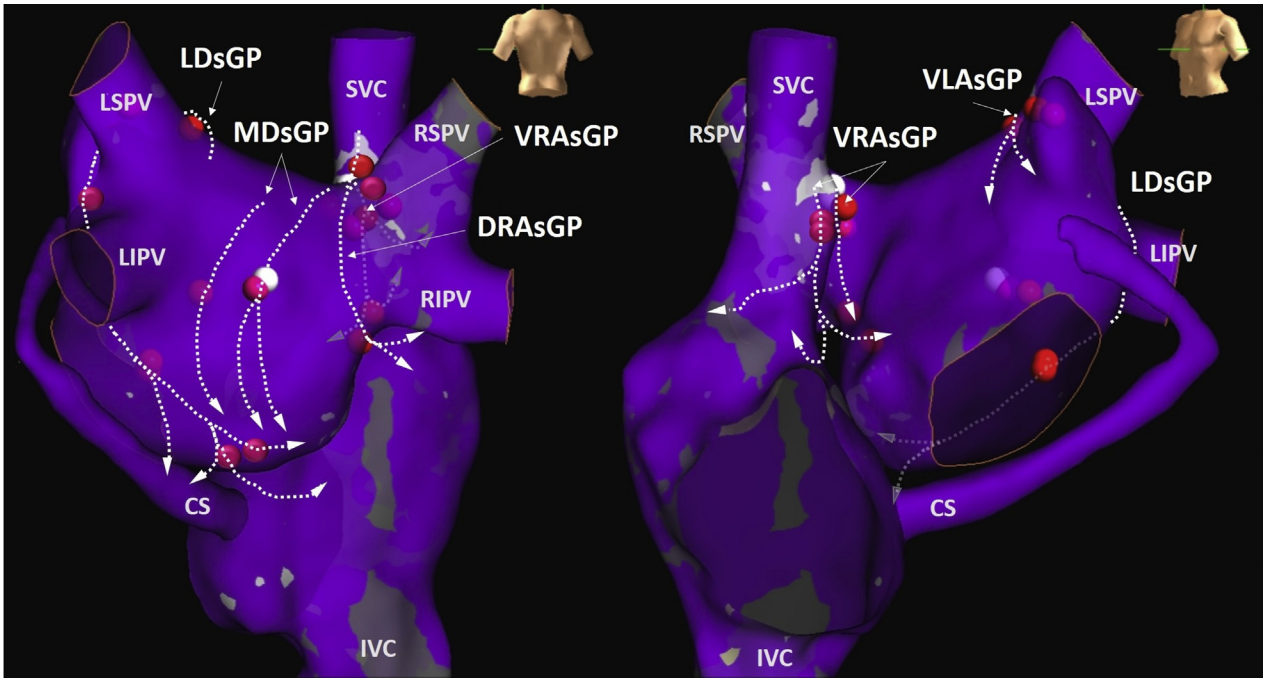
FIGURE 4 Schematic Drawing of the Location, Course, and Innervation Regions of the LDsGP, MDsGP, VRAsGP, DRAsGP, and VLAsGP on 3-Dimensional Mapping



The post-ganglionated nerves of the ventral right atrial ganglionated subplexus (VRAsGP) extended mostly into the ventral atrial regions, and some of these nerves may innervate the sinoatrial node, as well as penetrate the lower part of the interatrial septum. Post-ganglionated nerves of the ventral left atrial ganglionated subplexus (VLAsGP) may be observed to extend to the ventral inferior left atrial region, where they merge with the post-ganglionated nerves of the ventral right atrial ganglionated subplexus. Most of the post-ganglionated nerves of the left dorsal ganglionated subplexus (LDsGP) pass through the left dorsal coronary sulcus and spread onto the dorsal surface of the left ventricle. Although a part of the post-ganglionated nerves of the middle dorsal ganglionated subplexus (MDsGP) traverses the coronary sulcus and spreads onto the dorsal surface of both ventricles, part of the nerves passes superficially to the zone of the crux cordis along the coronary sulcus and approaches the post-ganglionated nerves of the dorsal right atrial sGP. The post-ganglionated nerves of the dorsal right atrial ganglionated subplexus (DRAsGP) spread widely into the dorsal and lateral right atrium, including the sinoatrial nodal region and the superior surface of the right atrial appendage. Please compare the distribution of the intrinsic cardiac ganglionated nerve subplexuses with **Figure 3**. CS = coronary sinus; other abbreviations as in **Figures 1 and 3**.

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