Major autonomic pathways to the aatria and S-A and A-V nodes of the canine heart

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GEIS, W. PETER, M. P. KAYE, AND W. C. RANDALL. Major autonomic pathways to the aatria and S-A and A-V nodes of the canine heart. Am. J. Physiol. 224(1): 202-208. 1973.—To demonstrate the course and distribution of autonomic nerves to the aatria and S-A and A-V nodes, individual mediastinal cardiac nerves were electrically stimulated prior to and following each of 9 paracardiac surgical procedures in mongrel dogs. Sympathetic innervation of the S-A node was along the superior vena cava (SVC), the interatrial grooves (IAG), and around the great arteries. Parasympathetic pathways entered the S-A node along the SVC, superior left atrium (LA), and IAG. Right-sided sympathetic fibers to the A-V node traversed the great arteries and the inferior left atrium (ILA). Fibers of left-sided origin entered at the junction of inferior vena cava (IVC) with ILA, along the great arteries, and in the ventro-lateral cardiac nerve. Parasympathetic pathways to the A-V node entered along IVC-ILA junction, and along the superior LA. Atrial sympathetic innervation was along the SVC, superior LA, and great arteries. Parasympathetic atrial innervation was along the SVC, great arteries, superior LA, IAG, and IVC-ILA junction.

METHODS

Seventeen mongrel dogs were preanesthetized with phencyclidine hydrochloride (2 mg/kg im) and anesthetized with α-chloralose (80 mg/kg iv). Positive-pressure respiration was instituted, the chest was opened bilaterally, and a pericardial cradle constructed. Walton-Brodie strain-gauge arches were sutured to the right atrium (RA), left atrium (LA), and right ventricle (RV). Systemic pressure was monitored from a cannula in the femoral artery. All data were recorded on a model 7 Grass polygraph.

Both vago-sympathetic trunks were transected in the neck, the anterior and posterior ansae were divided bilaterally at their origin from the stellate ganglia, and the mediastinal cardiac nerves were isolated for subsequent stimulation. The nerves were designated by the terminology of Mizeres (6) as the anterior and posterior ansae, recurrent cardiac, cranio-vagal, caudo-vagal, stellate cardiac, ventrolateral cardiac (VLCN), ventromedial (VMCN), innominate, cervical vago-sympathetic trunks, and the thoracic vagus nerves. Each of these nerves with cardiac efferent distribution were electrically stimulated supramaximally with square-wave impulses of 10 Hz, 5 msec duration, and 6 v, prior to and after each of the following interventions.

Surgical ablation procedures were performed to selectively interrupt the extrinsic cardiac nerve pathways as they enter the heart (2). Figure 1 depicts the interventions: I) transection and reanastomosis of the intrapericardial superior vena cava (SVC) from its junction with the superior margin of the left atrium to the anterior SVC; II) transection and reanastomosis of the lateral portion of the intrapericardial SVC from the anterior SVC to the level of the right superior pulmonary vein; III) excision of all neural elements, epicardium, and areolar tissue in the interatrial groove (IAG) from the right superior pulmonary vein to the right inferior pulmonary vein; IV) transection and reanastomosis of the inferior border of LA from the junction of the inferior vena cava (IVC) with the LA to the left inferior pulmonary vein, V) transection and reanastomosis of the lateral border of LA from the left inferior pulmonary vein to the left superior pulmonary vein; VI) transection and reanastomosis of the superior border of LA in the transverse sinus from the left superior pulmonary vein to the SVC; VII) circumferential transection of adventitia and all neural elements on the left half of the main pulmonary artery; VIII) circumferential transection of adventitia and all neural elements on the right half of the pulmonary artery and on the left half of the ascending aorta; IX) transection of the VLCN as it enters the heart at the origin of the left superior pulmonary vein and circumferential transection of adventitia on the right half of the ascending aorta. In six experiments the procedures were performed in the reverse order. In the remaining five experiments the areolar tissue and neural elements located at the junction of
the IVC with the inferior margin of the LA were excised after procedures I, II, and III. Although this dissection was in most instances (12 animals) performed as a part of intervention IV, evidence accumulated to suggest that the majority of fibers transected on the inferior left atrial surface actually lie in the IVC-LA junction. Hence these five experiments were conducted to definitely localize the neural pathways to this area.

Recognizing that the exact sites of pacemaker activity may shift from the S-A and A-V nodes to nearby specialized tissue, the following definitions are used in this manuscript for the purpose of simplicity and clarity:

Whenever nerve stimulation resulted in an increment in heart rate accompanied by electrical activity and contraction of RA and LA preceding RV electrical activity and contraction, the interpretation was sinus acceleration and sympathetic innervation of sinus node; whereas, if RA contraction and electrical activity occurred at the same time, or following RV electrical activity and contraction, the designation was A-V rhythm and sympathetic innervation of the A-V node. When nerve stimulation resulted in a decrease in atrial rate, the interpretation was sinus bradycardia or arrest and cholinergic innervation of the sinus node; when stimulations caused no change in atrial rate but slowing of the RV rate or complete RV arrest, the response was interpreted as cholinergic innervation of A-V node.

RESULTS

Sinus Node Sympathetic Innervation

Prior to ablation procedures, the heart rate (HR) averaged 139 beats/min (range 128–171). Electrical stimulation of the following nerves resulted in sinus tachycardia in all experiments: right anterior ansa (HR = 253, range 222–300), right posterior ansa (HR = 233, range 220–261), and right stellate cardiac (HR = 249, range 220–272). Stimulation of the left posterior ansa elicited sinus tachycardia in 14 of 17 experiments (HR = 189, range 162–222), while left anterior ansa stimulation elicited the response in only 8 of 17 experiments (HR = 191, range 170–214); recurrent cardiac nerve in 6 of 17 (HR = 252, range 200–286); innominate nerve in 5 of 17 (HR = 156, range 140–172); VMCN in 5 of 17 (HR = 161, range 140–181); and VLCN in 8 of 17 experiments (HR = 188, range 172–200). Following transection of the medial and lateral portions of the SVC, stimulation of the right anterior and posterior ansae, the recurrent cardiac, innominate, and right stellate cardiac nerves no longer produced sinus acceleration in any of the animals.

Sinus acceleration, however, continued to be observed during nerve stimulation of the left posterior ansa in 2 of 17 experiments (HR = 152 and 160) and during stimulation of the left anterior ansa in 2 of 17 experiments (HR = 140 and 152). After interruption of neural elements along the great vessels, these responses no longer occurred. However, stimulation of the VLCN continued to elicit sinus acceleration in 2 of 17 experiments (HR = 152 and 193), and the VMCN did so in 1 of 17 experiments (HR = 172). These responses were interrupted following interruption of neural elements in the interatrial groove.

Sinus Node Parasympathetic Innervation

Initial electrical stimulation of the following nerves caused a decreased atrial rate and contractile force in all animals: right vagosympathetic trunk (HR = 55, range 0–90); left vagosympathetic (HR = 61, range 30–100); right thoracic vagus (HR = 82, range 40–120); left thoracic vagus (HR = 70, range 30–100); and craniovagal nerve (HR = 89, range 60–104). Further, recurrent cardiac nerve stimulation resulted in a decrement in atrial rate in 8 of 17 experiments (HR = 92, range 56–120); while the caudovagal nerve did so in 16 of 17 experiments (HR = 82, range 30–125). Stimulation of the remaining nerves did not induce decreased atrial rate.

Following transection of the SVC, atrial slowing did not occur during the majority of nerve stimulations. However, on occasion, slowing persisted and this response was interrupted as follows: right vagosympathetic trunk required interatrial groove dissection on two occasions; left vagosympathetic trunk required IAG dissection on one occasion and transection of the superior LA on one occasion; right thoracic vagus nerve required IAG dissection on two occasions; left thoracic vagus nerve required IAG dissection on two occasions and transection of the superior LA on two occasions; craniovagal nerve required transection of the superior LA on two occasions; and caudovagal nerve required transection of the superior LA on two occasions. Subsequent to these interventions, electrical stimulation of cardiac nerves never resulted in atrial bradycardia or arrest.
Figure 2 depicts, in the control column, a decrease in HR from 141 to 109 beats/min as well as depression in RA and LA contractile force (RAF and LAF) during electrical stimulation of the left cervical vagus nerve. After transection of the medial SVC (left SVC column), HR was no longer altered by stimulation; however, depression of contractile force in both atria continued. These results indicate that parasympathetic fibers from this nerve reach the region of the sinus node along the medial SVC and that most negative inotropic components to the atria enter along other routes.

**Atrial Innervation: Sympathetic**

Initial electrical stimulation of the following nerves resulted in augmentation in contractile force in both atria in all experiments: right anterior and posterior ansae, left anterior and posterior ansae. In contrast, stimulation of the VLCN resulted in augmentation of LA contractile force in all animals with augmentation in the RA in only 7 of 17 experiments. VMCN stimulation produced RA augmentation in 8 of 17 experiments and augmentation in LA in only 3 of 17. Right stellate cardiac nerve stimulation caused RA augmentation in 14 of 17 and in LA in only 3 of 17 experiments. Recurrent cardiac nerve stimulation elicited augmentation in the RA in 10 of 17 and in the LA in 4 of 17 experiments, whereas the innominate nerve induced augmented RA contractile force in 3 experiments, but never in the LA. Stimulation of the remaining nerves did not result in augmentation of contractile force in either atrium.

**Right atrium.** On all occasions, augmentation of RA contractile force due to stimulation of the right stellate cardiac nerve was interrupted by transection of the SVC. Innominate nerve and recurrent cardiac nerve augmentation of RA was interrupted on all occasions by transection of the SVC or transection of the superior LA. Augmentation of the RA during stimulation of the VMCN and VLCN was abolished by transection of the SVC and/or by interruption of nerves along the root of the great vessels. Only rarely did a single intervention interrupt the positive inotropic response to stimulation of the right or left anterior and posterior ansae. The magnitude of inotropic response to stimulation of each of these nerves was usually depressed after any one of the following interventions: transection of the SVC, transection of the superior LA, or interruption of nerves along the root of the great vessels. Conversely, following all three of these procedures, neurally induced augmentation of contractile force in the RA was invariably abolished.

**Left atrium.** Interruption of the inotropic response in LA to stimulation of the right stellate cardiac and the recurrent cardiac nerves was accomplished by transection of the SVC. The response to VMCN stimulation was partially interrupted by transection of the superior LA, but usually required transection of the VLCN at the left superior pulmonary vein for total ablation of inotropic response. LA inotropic responses to stimulation of the right and left ansae were interrupted by combined transection of the superior LA and those nerves

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**FIG. 2.** Recordings prior to and during stimulation (indicated in line 2) of left cervical vagus. BP = systemic blood pressure; LAF = left atrial contractile force. Control = before transection; LT SVC = procedure I; RT SVC = procedure II; LT PA = procedure VII.
along the root of the great vessels. On one occasion, responses to stimulation of the right posterior and left anterior ansae were not completely interrupted until transection of the inferior LA.

Atrial Innervation: Parasympathetic

In a majority of experiments a decrease in contractile force occurred in both atria during electrical stimulation of the right and left thoracic vagus nerves, the right and left cervical vagosympathetic trunks, the craniovagal nerve, and the caudovagal nerve. Stimulation of the recurrent cardiac nerve resulted in depression of RA and LA contractile force in 11 of 17 experiments, while stimulation of the innominate nerve caused decreased contractile force in the RA in 5 animals and in the LA in 3 animals.

Right atrium. The negative inotropic response in RA to stimulation of the left thoracic vagus, left cervical vagosympathetic trunk, craniovagal nerve, recurrent cardiac nerve, and innominate nerve was invariably abolished following a combination of two procedures: 1) transection of the SVC, and 2) transection of nerves along the roots of the great vessels. Either intervention alone generally resulted in a lesser response, but rarely in complete abolition. The negative inotropic response of RA to stimulation of the right cervical vagosympathetic trunk and caudovagal nerve was also deleted by transection of the nerves along the root of the great vessels and transection of the SVC. However, in three additional experiments, dissection of the interatrial groove was necessary to completely abolish the response to these two nerve stimulations. Right thoracic vagus responses were not eliminated by transections along the root of the great vessels. In contrast, they were abolished in the majority of experiments by combined transection of the SVC and dissection of the interatrial groove. In three experiments, these responses persisted until the added transection of the inferior margin of LA was performed.

Left atrium. The negative inotropic response of LA during stimulation of the recurrent cardiac nerve was interrupted on all occasions after transection of the SVC, whereas the response to innominate nerve stimulation was interrupted by transection of the superior I.A. The response to stimulation of the right cervical vagosympathetic trunk and the craniovagal nerve was also generally interrupted following transection of the SVC. However, on two occasions, the response to right vagosympathetic trunk stimulation was not totally abolished until nerves at the root of the great vessels were transected. In one experiment, the response to craniovagal nerve stimulation was totally eliminated following dissection along the great vessels. The response to left cervical vagosympathetic trunk and left thoracic vagus nerve stimulation was abolished following transection of the superior I.A in the majority of instances. However, in two experiments, dissection around the great vessels was necessary to ablate the response to left vagosympathetic stimulation, and in one experiment the same procedure was necessary to interrupt the response to left thoracic vagus nerve stimulation. The LA response to caudovagal nerve and right thoracic vagus nerve stimulation required both transection of the SVC and the inferior margin of the LA for its elimination. Moreover, in one experiment, dissection at the root of the great vessels was also required to totally interrupt the response to caudovagal nerve stimulation.

Note in Fig. 2 that after medial (Left) SVC transection, RA and LA contractile force (RAF and LAF) continued to be depressed during stimulation of the left cervical vagus nerve. However, after transection of the lateral SVC (right SVC column), RA contractile force was no longer depressed while LAF continued to be depressed. The latter was eliminated by dissection along the pulmonary artery (left PA column). Thus, parasympathetic fibers from this nerve to RA enter the heart along the lateral side of the SVC, while parasympathetic fibers to the LA enter along the left side of the main pulmonary artery.

A-V Node Innervation

Prior to surgical intervention, electrical stimulation of each of the cardiac nerves generally resulted in either sinus acceleration or deceleration (see Sinus Node Innervation). A majority of sympathetic and parasympathetic nerve pathway responses to the sinus node enter the heart along the SVC, and it is of interest that A-V nodal rhythms were demonstrated in nearly all of the 11 experiments in which transection of the SVC was the first intervention performed. Following transection of the SVC, acceleration or slowing of the A-V node was demonstrated during nerve stimulation with no longer any neural influence on the sinus node region. In the few experiments in which sinus node responses persisted after SVC transection, neural influences upon the A-V node were not demonstrated until the remainder of sinus node innervation was interrupted (see Sinus Node Innervation).

Sympathetic innervation. After interruption of sympathetic pathways to the sinus node, A-V tachycardia was demonstrable in all 11 animals with an average rate of 199/min (range = 170-240). Left anterior ansa and VLCN stimulation resulted in A-V tachycardia in all of these animals, while left posterior ansa did so in eight experiments, right anterior ansa in seven, and right posterior ansa in six experiments. Stimulation of the innominate, recurrent cardiac, and craniovagal nerves each produced the response in two experiments, whereas VMCN resulted in A-V tachycardia in three experiments. The caudovagal and right thoracic vagus nerves elicited the response in only one of the 11 animals.

The A-V nodal responses to electrical stimulation of the caudovagal, right thoracic vagus, and innominate nerves were interrupted after transection of the inferior margin of the LA on all occasions. The responses to stimulation of the recurrent cardiac, VMCN, and craniovagal nerves were interrupted following thorough dissection at the root of the great vessels. The right anterior ansa, right posterior ansa, and left posterior ansa each exhibited a bimodal distribution to the A-V node. Transection at the root of the great vessels interrupted the A-V tachycardia to right anterior ansa and right posterior ansa stimulation in two experiments, and to left posterior ansa stimulation in four experiments. Further abolition of the A-V response occurred after transection of the inferior LA to left and right posterior ansa stimulation in four experiments. While the response to right anterior ansa stimulation was interrupted by this procedure on five occasions, the A-V response to left anterior ansa stimulation was interrupted following transection of the inferior LA in six experiments. In three additional experiments, transection of the nerves at the root of the great vessels was necessary to completely abolish this response. In the remaining two experi-
ments, the response was not interrupted until transection of the VLCN. The A-V response to stimulation of the VLCN was interrupted after transection of the inferior LA in seven experiments. In the remaining four experiments, both transection of the nerves at the root of the great vessels and transection of the VLCN at the left superior pulmonary vein were required to completely interrupt the response. After either of the two latter procedures, the magnitude of the response was usually decreased, but both procedures were necessary for its abolition.

Figure 3 depicts cardioacceleration (from 146 to 250/min) during electrical stimulation of the right anterior ansa (control column). Electrical and mechanical activation of RA (BE (RA) and RAF) precede comparable activation of RV (BE (RV) and RVF). Following transection of SVC (SVC transection column), electrical stimulation elicited an increase in HR to 190/min with electrical and mechanical activation of RA and RV occurring simultaneously. Thus, the sympathetic fibers from this nerve to the sinus node enter the heart along the SVC and interruption of these neural elements unmasked A-V tachycardia. The sympathetic fibers to the A-V nodal region were interrupted following transection of the junction of the inferior vena cava with the inferior margin of the LA (IVC-ILA junction column). Note that in the right column, stimulation resulted in slight cardioacceleration, but electrical and mechanical activation of the RA continued to occur 70 msec prior to that in RV.

**Parasympathetic innervation.** Parasympathetic innervation of the A-V nodal region was demonstrated in all animals in which transection of the SVC was the first procedure performed. Following effective parasympathetic denervation of the sinus area, stimulation of parasympathetic nerves resulted in slowing or cessation of ventricular rate accompanied by no change in atrial rate. In all 11 animals, A-V innervation was demonstrated during stimulation of the right and left thoracic vagus nerves, and right and left vagosympathetic trunks. A-V parasympathetic innervation was also demonstrated during stimulation of the caudal vagal nerve in four experiments, during stimulation of the cranial vagal nerve in two experiments, and during stimulation of the recurrent cardiac nerve in one experiment. The remaining cardiac nerves did not parasympathetically innervate the A-V nodal region.

In all experiments, the A-V nodal response to parasympathetic stimulation was interrupted following transection of the superior margin of the LA and/or dissection at the inferior margin of LA. Interruption of functional A-V nodal block due to nerve stimulation was accomplished by transection of the superior LA as follows right thoracic vagus nerve stimulation in three experiments, to right cranial vagosympathetic trunk stimulation in two experiments, to left cervical vagosympathetic nerve stimulation in five experiments, and in one experiment each to left thoracic vagus, cranio- and caudal vagal nerve stimulation. However, in many experiments, transection of the superior LA did not totally interrupt inhibitory fibers to the A-V nodal area. In these experiments (listed below) transection of the inferior LA invariably interrupted the A-V response to stimulation of each of the nerves. The left thoracic vagus nerve response was interrupted in 10 experiments, the right thoracic vagus nerve response was interrupted in 8 experiments, the right cervical vagosympathetic trunk response in 9 experiments, the left cervical vagosympathetic trunk in 5, the cranio- and caudal vagal, and recurrent cardiac nerve response each in 1 experiment.

**DISCUSSION**

Mizeres (6, 7) has anatomically described the only autonomic nerve that is large enough to be readily traced to the canine heart, the ventrolateral cardiac nerve. This nerve reaches the pericardium as it descends anterior to the left pulmonary artery and left superior pulmonary vein. As it penetrates the pericardium it profusely branches over the left wall of the LA. Randall et al. (9) have physiologically characterized the thoracic VLCN as sympathetic and innervating the left atrium as well as the lateral and posterior walls of the left ventricle. Kaye et al. (3, 4) have described other major sympathetic sites of neural entry to both ventricles to be subjacent to the adventitia of the aorta and pulmonary artery. These nerve pathways innervate the anterior walls of both ventricles and travel from base to apex (1, 10). These investigators have further demonstrated that the nerves entering along the great vessels also innervate the upper portion of the interventricular septum (9). The current investigation describes a third group of sympathetic
FIG. 4. Right lateral view of heart demonstrating right-sided sympathetic innervation of A-V nodal region.

FIG. 5. Left lateral view of heart demonstrating right-sided sympathetic innervation of the A-V nodal region. VMCCN = ventromedial cervical cardiac nerve; VLCCN = ventrolateral cervical cardiac nerve.

FIG. 6. Left lateral view of heart demonstrating left-sided parasympathetic innervation of A-V nodal region.

FIG. 7. Right lateral view of heart demonstrating right-sided parasympathetic innervation of A-V nodal region.

FIG. 8. Right lateral view of heart demonstrating sympathetic innervation of sinus node region.

FIG. 9. Right lateral view of heart demonstrating parasympathetic innervation of sinus node region.
nerves to the ventricles that descend posterior to the heart and enter the myocardium at the junction of the inferior vena cava with the left atrium. These nerves provide sympathetic innervation to the posterior walls of both ventricles and to the interventricular septum. Furthermore, they provide additional sympathetic and parasympathetic innervation of the A-V nodal region.

These structure-function experiments are summarized and the resulting patterns of cardiac innervation more clearly schematized in Figs. 4-9. The A-V nodal region is innervated by sympathetics from the right side by nerves that course along the great vessels and at the junction of the IVC with the left atrium. (Fig. 4). Left-sided sympathetic nerves reach the nodal region along similar pathways as well as in the VLN (Fig. 5). Parasympathetic innervation to the A-V nodal area in all instances is along the superior left atrium and at the junction of the left atrium with the inferior vena cava (Figs. 6, 7).

The sinus node region receives sympathetic innervation predominantly by way of fibers coursing along the SVC, with other pathways noted along the great vessels and in the interatrial groove (Fig. 8). Parasympathetic fibers to this region are interrupted by section of the SVC, superior LA, and interatrial groove (Fig. 9).

Positive inotropic response of the right atrium to sympathetic nerve stimulation is abolished by section of the SVC, superior LA, and great vessels. Sympathetic pathways to the left atrium are similar with additional fibers noted in the VLN and the junction of the left atrium with the inferior vena cava.

Negative inotropic atrial response to nerve stimulation is abolished for the right atrium by transection of the SVC, dissection around the great vessels and the interatrial groove and occasionally at the IVC-LA junction. Parasympathetics to the left atrium are interrupted by transection of the SVC and superior left atrium by dissection around the great vessels and at the IVC-LA junction.

These data demonstrate the distribution of individual autonomic nerves to the atria and the S-A and A-V nodal regions and the precise projection of these nerves onto the heart. The physiological consequences of interruption of these neural pathways have been previously discussed (2, 5, 8). The location of the pathways of these neural elements must be considered when cardiac manipulation and the technical implantation of recording devices for physiological studies are undertaken. The redundancy in regional nerve supply is of particular interest and must be taken into account in the evaluation of cardiac denervation, with subsequent reinnervation, following any method of denervation short of complete cardiac extirpation.

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REFERENCES


