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# Complex Cardiovascular Responses to Vagosympathetic Stimulation[1] (37838)

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Electrical stimulation of the vagus nerve is a common procedure in experimental physiology, generally performed in association with demonstrations of efferent neural regulation of the heart. The resulting bradycardia, depressed atrial contractility, and inhibition in conductivity, particularly through the AV node, are well-recognized. However, such experiments are frequently characterized by lack of appreciation of the presence and function of afferent nerves within the trunk, and when recognized they are almost universally associated with reflex depression in cardiac activity. In some animals, the afferent nerves appear to aggregate into a separate "depressor nerve," and in man, may run in cardiac branches of the laryngeal nerve (1).

A few recent studies suggest that atrial receptors located in the pulmonary vein–atrial junctions exert an excitatory influence, particularly with regard to heart rate (2), but the responses can not be considered strongly pressor. In fact, Edis, Donald, and Shepherd (3) were unable to clearly confirm the accelerator response to distension of these receptors except when initial heart rates were low. Oberg and Thoren (4) recently reported a low, spontaneous activity in nonmedullated afferents from cardiac receptors which were associated with powerful depressor cardiovascular responses. Such impulse traffic was easily obscured by the high-frequency rhythmic discharges in medullated fibers (5). We are unable to cite evidence for strongly pressor responses associated with excitation of vagal afferent fibers.

Afferent vagal cardiac impulses may thus be introduced into the brainstem via both medullated and nonmedullated afferents, with activation of efferent impulses coursing back to the heart via the same (ipsilateral and contralateral) vagi from whence the afferents came. Changes in heart rate, cardiac contractility, and peripheral resistance, supplemented by alterations in adrenal medullary secretions of catecholamines, may lead to summated circulatory responses. Responses generally interpreted to result from direct stimulation of efferent vagal inhibitory fibers are, in fact, due to complex reflex interactions involving afferent as well as sympathetic and parasympathetic nerves. This report illustrates these interactions during experimental stimulation of the vagosympathetic trunk in the dog, and includes important evidence for pressor reflexes associated with vagal afferents.

*Materials and Methods.* Studies were carried out on 18 anesthetized (alpha chloralose, 60 mg/kg and phencyclidine HCl, 2.0 mg/kg) open-chest dogs. Bipolar electrodes were applied to the intact cervical vagosympathetic trunk and subsequently to the central and distal ends of the severed trunk, before and after transection of the contralateral cervical vagosympathetic trunk. Stimulation parameters were varied between 10–40 Hz, 2–5 msec, and 4–8 V, as delivered from a Grass model S4 stimulator. Recordings were made of the electrocardiogram (ECG) and femoral arterial blood pressure (BP). Contractile force was also

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recorded from 1-cm segments of myocardium on the right atrium (RA), right ventricular conus (RVC), right ventricular sinus (RVS), left atrium (LA), left ventricular anterior (LVA), and left ventricular lateral (LVL) surfaces. The isometric recordings of contractile force were made from Walton–Brodie strain gauge arches upon a Model 7 Grass Polygraph or a Model R Offner Dynograph; each gauge was sutured so that it was oriented parallel to the underlying muscle fibers in order to obtain maximal contractile responses.

Figure 1 illustrates the cardiac responses to electrical stimulation of the left cervical vagosympathetic trunk. Panel A shows typical inhibitory changes induced on five different cardiac locations as revealed by strain gauge arches, together with systemic arterial pressure. The intact trunk was stimulated (10 Hz, 5 msec, 4 V) for a period of 14 sec with bradycardia appearing within one cardiac cycle after onset of stimulation. Slowing was more prominent in the ventricle than in the atria, thus revealing 2:1 atrioventricu'ar block. Suppression in atrial contractility, greater in LA than in RA, progressively developed. Some inhibition in ventricular contractile force (both right and left) became apparent with restoration of heart rate immediately upon cessation of stimulation. Blood pressure was depressed, but in surprisingly small amount, during the stimulation. Recovery was characterized by progressively increasing contractile force on all areas, together with supraventricular tachycardia. The latter spontaneously subsided some 10 sec after onset.

All of these changes could ordinarily be attributed to direct efferent consequences of vagal stimulation, with some possible concern for the relatively minor degree of bradycardia and moderate decline in blood pressure.

Panel B demonstrates responses to identical stimulation of the distal end of the transected left cervical vagosympathetic trunk in the same animal. Resulting bradycardia was more pronounced with atrioventricular block and profound suppression in atrial contractile force. Again, the latter was greater in LA than in RA. Inhibition in contractile force (note amplitude of force changes during early recovery period) was also greater in left than right ventricular segments. Blood pressure fell much more markedly than shown in panel A during periods of asystole.

In panel C, the inhibitory changes were

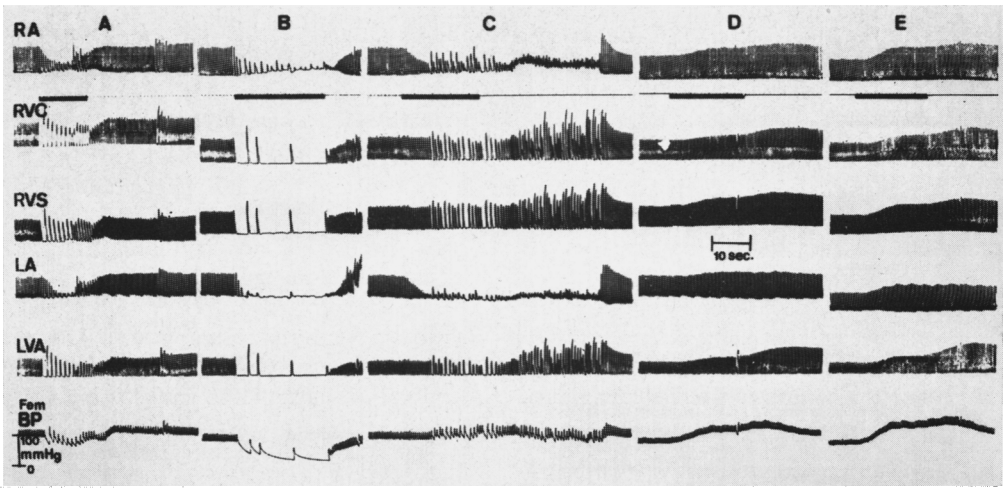


FIG. 1. Changes in cardiac contractile force, heart rate, and arterial blood pressure during electrical stimulation (10 Hz, 5 msec, 4 V) of the intact (panel A), distal (B), and central (C) ends of the left cervical vagosympathetic trunk of a dog. Panel D resulted from stimulation of the left central vagosympathetic trunk in the same animal after the additional transection of the right cervical vagosympathetic trunk. Panel E illustrates the response to identical stimulation of the right central vagosympathetic trunk.

more nearly comparable to those observed in panel A and were elicited by identical stimulation of the central end of the transected left cervical vagosympathetic trunk. The onset of bradycardia and inhibition in atrial contractile force appeared on the second or third beat following onset of stimulation, well in advance of any alteration in systemic arterial blood pressure. Changes in arterial pressure, therefore, can not be implicated in the interpretation of these reflex responses. However, a primary difference in the responses of panel C (from those in panel A) resides in the systemic arterial pressure which, in spite of comparable cardiac slowing, was actually elevated above control levels.

Another striking feature of the changes in panel C is the reflex development of atrial fibrillation and associated ventricular dysrhythmias some 8–10 sec after cessation of stimulation. This observation is significant in that it illustrates a severe cardiac dysrhythmia induced by *reflex* neural influences upon the heart. Spontaneous reversion occurred 10 sec later.

The right cervical vagosympathetic trunk was then transected, and the left central vagosympathetic trunk again excited (panel D) in precisely the same manner as in panel C. In the absence of vagal feedback pathways to the heart, the responses were entirely pressor with prompt elevations in blood pressure and myocardial segment contractile force. Heart rate accelerated from 135 to 150 beats/min. Approximately 20 sec after onset of stimulation, a secondary augmentation in contractile force and rise in blood pressure suggests activation of humorally induced pressor changes through adrenal medullary secretion.

Panel E shows entirely comparable reflex changes elicited by electrical stimulation of the central end of the right cervical vagosympathetic complex. Subsequent excision of the right and left stellate ganglia markedly attenuated the pressure elevation and eliminated the initial augmentations in contractile force. The delayed (adrenal medullary) elevations in force were retained.

Figure 2 illustrates the excitation of both efferent and afferent nerves within the cervical vagosympathetic trunk of two different animals. Panel A shows responses to stimulation of the intact left vagosympathetic trunk before, while panel B illustrates responses to identical stimulation after surgical section of the contralateral (right) cervical vagus. Both right and left atria responded with distinct suppression in contractile force concurrently with marked bradycardia. The ventricles tended to show augmentation in contractile force, most clearly evident in the left ventricular segments. In spite of the markedly slowed heart rate, however, systemic arterial blood pressure became severely elevated during the period of stimulation, and remained so for a prolonged interval following cessation of stimulation. It is apparent that the bradycardia was more sustained while both vagi remained intact (panel A) than after unilateral vagotomy (panel B). These results clearly illustrate the simultaneous implication of both afferent and efferent neural mechanisms, and include components of both the sympathetic and parasympathetic divisions of the autonomic cardiac nerves. Panel C illustrates responses to electrical excitation of the central end of the right cervical vagosympathetic trunk after decentralization of both vagi. The overall responses included reflex acceleration in heart rate (from control of 160 to 220/min), prompt augmentation in contractile force on all myocardial segments, and profound elevation in systemic arterial blood pressure. Thus, it is clear that afferent fibers contained within the vagosympathetic trunk are capable of inducing profound pressor responses which simultaneously implicate depressor efferent pathways within the descending vagus, together with pressor pathways in sympathetic cardiac, vasomotor, and adrenal medullary motor nerves.

In 18 experiments, such combined excitatory and inhibitory responses have been elicited through simultaneous stimulation of efferent and afferent vagosympathetic pathways in the dog. Varying degrees of reflex inhibitory bradycardia ranged from complete cardiac standstill and severe atrioventricular blockade to an occasional animal with only slight sinus slowing in heart rate. Systemic arterial blood pressure alterations also

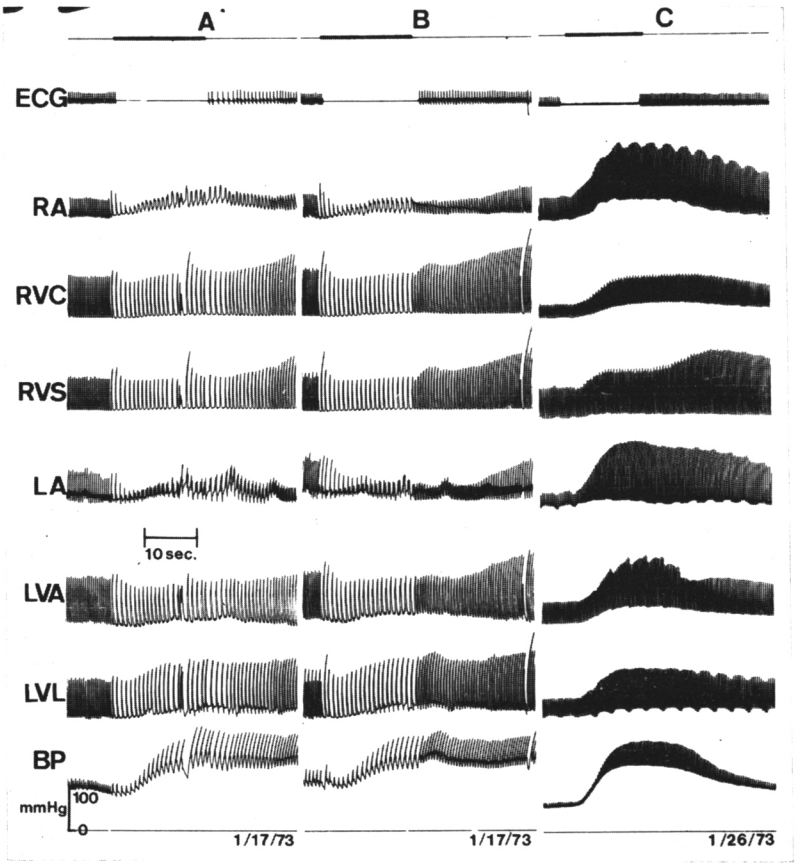


FIG. 2. Concurrent pressor and depressor responses to electrical stimulation (40 Hz, 2 msec, and 5 V) of the left vagosympathetic trunk while both cervical vagi were intact (panel A), and after surgical transection of the contralateral vagus (panel B). Panel C illustrates responses to identical stimulation of the central (afferent) end of the cervical vagosympathetic trunk in the bilaterally vagotomized animal. Note the combined responses including inhibition in atrial contractile force, augmentation in ventricular contractile force, cardiac slowing, and elevation in systemic arterial blood pressure.

varied, some animals showing systolic pressures well in excess of 300 mm Hg during central excitation of the cut cervical vagosympathetic trunk. A few displayed moderate hypotension, with accompanying suppression in myocardial contractility, presumably due to withdrawal of sympathetic influences upon the heart.

Table I summarizes the responses to electrical stimulation of the cervical vagosympathetic trunk in 11 dogs when both vagi were intact (column I), during stimulation of the central (afferent) end of the vagus when the remaining vagus was intact (column II), and finally, during excitation of the central vagus after bilateral vagotomy (column III). All of the animals showed negative chronotropic action during stimulation of the intact vagi, but only one-half showed a decline in mean arterial blood pressure (the other half showing elevations in blood pressure). While a majority of animals showed a reduction in heart rate in the presence of a single intact vagus (column II), the decrease was distinctly less marked than in column I. Only three animals showed a reduction in mean arterial pressure while clear elevations in pressure occurred in all of the remainder (column II). Stimulation of the central (afferent) end of the cervical vagus in animals with bilateral cervical vagotomy (column III) elicited little or no

change in heart rate in four animals but produced clear-cut elevations in heart rate in six. Marked elevations in arterial pressure occurred in all but two of the bilaterally vagotomized animals, and in some instances the elevations were to remarkably high levels (animals Nos. 3 and 9). Thus, it is clear that considerable variation in direction and intensity of the pressor response to stimulation of the afferent component of the cervical vagosympathetic trunk occurs from animal to animal. However, when the efferent limb of the vagal reflex is eliminated (bilateral vagotomy), the pressor component emerges as the more powerful response in a majority of animals.

*Discussion.* While both afferent and efferent pathways in the vagi are generally recognized, and both pressor and depressor mechanisms of cardiovascular control are well-established, their simultaneous and opposing activation are not commonly appreciated. Neither is the potentially high level of hypertension generally recognized. Known afferent systems feeding into the thoracic vagus include aortic, pulmonary atrial, and ventricular mechanoreceptors which provide information on each heart beat. Also, arterial chemoreceptors and lung inflation and deflation receptors convey information about respiratory performance. Aortic arch baroreceptors are major cardiovascular mechanoreceptors involved although pulmonary artery receptors are known to be located in the main branch of the artery, and such units are active at normal pressures (6). Receptors in both atria generate a variety of impulse traffic patterns associated with the cardiac cycle (7). Ventricular receptors signal changes in systolic ventricular tension or in extremes of ventricular loading and pharmacologic stimulation (8, 9). Arterial chemoreceptors are excited by changes in $PaO_2$, $PaCO_2$, and blood flow. Receptors that signal alterations in pulmonary dynamics give origin to a very large group of vagal afferent fibers and probably contribute to cardiovascular reflex activity (10).

Strong electrical stimulation of these afferent pathways in the vagal nerves obviously occurs concurrently with excitation of known efferent parasympathetic pathways

TABLE I.[a]

| | I | | | II | | | III | | |
|---|---|---|---|---|---|---|---|---|---|
| | Both vagi intact | | | One vagus intact | | | Neither vagus intact | | |
| Animal | Heart rate | Blood pressure | Mean | Heart rate | Blood pressure | Mean | Heart rate | Blood pressure | Mean |
| 1 | 190–90 | 145/110—195/125 | +32 | | | | 200–200 | 160/120—205/155 | + 40 |
| 2 | 150–0 | 90/65—25 | —52 | 125–135 | 105/75—85/65 | — 15 | 115–115 | 125/100—75/50 | — 50 |
| 3 | 150–0 | 90/65—25 | —52 | 150–0 | 90/65—25 | — 52 | 150–230 | 65/40—225/155 | +138 |
| 4 | | | | 130–0 | 155/100—10 | —177 | 155–175 | 150/105—265/160 | + 78 |
| 5 | 130–40 | 120/95—225/125 | +68 | 145–20 | 130/105—225/125 | + 58 | 180–210 | 150/120—215/150 | — 47 |
| 6 | 150–70 | 85/65—75/50 | —13 | | | | 140–185 | 80/60—150/125 | + 67 |
| 7 | 190–0 | 105/85—30 | —65 | 150–110 | 105/85—135/110 | + 27 | | | |
| 8 | | | | 160–150 | 150/120—295/185 | + 75 | 160–160 | 150/120—225/185 | + 70 |
| 9 | 160–30 | 105/75—80/35 | —45 | 160–155 | 115/85—275/205 | +140 | 160–220 | 125/100—315/225 | +158 |
| 10 | 170–45 | 140/110—175/105 | +15 | 160–160 | 140/105—175/135 | + 33 | | | |
| 11 | 155–30 | 140/110—175/105 | +15 | 180–100 | 140/110—190/125 | + 30 | 185–190 | 150/120—205/155 | + 55 |
| Average | 157–38 | 116/90—123/75 | —5 | 151–92 | 125/94—151/110 | + 20 | 160–187 | 128/98—209/151 | + 67 |

[a] In each column, the initial values represent control while the final values represent peak (or minimal) values elicited by vagosympathetic stimulation. Mean blood pressure changes are shown as increases (+) or decreases (—) from control levels.

to the heart. Stimulation of the aortic, atrial, and ventricular mechanoreceptors is said to elicit reflex bradycardia, decreased peripheral resistance, and hypotension. In contrast, physiological stimulation of the aortic chemoreceptors elicits a rise in total peripheral resistance, sometimes accompanied by moderate bradycardia (11, 12). Thus, stimulation of the vagosympathetic afferents produces changes in autonomic effector activity including vagal efferents, cardiac sympathetic nerves, and constrictor nerves to many peripheral vascular beds and the adrenal medulla (13). The ultimate cardiodynamic responses to such experimental maneuvers then consists of the algebraic sum of multiple complex and sometimes opposing influences.

Histological examination of the primary cardiac nerves in both the cat and dog have revealed the presence of both myelinated and nonmyelinated fibers, and it is reasonable to presume that both kinds of fibers may be involved in transmitting impulse traffic to the brainstem from the many and varied receptors within and around the heart. Indeed, Oberg and Thoren (4) have recently differentiated such traffic in selected cardiac nerves and suggest that it is the nonmyelinated fibers and their associated receptors that play a primary role in the induction of powerful depressor reflexes. Selective stimulation of myelinated afferents induced moderate reflex rises in blood pressure, acceleration in heart rate, and vasoconstriction in skeletal muscle and kidney vessels (5). Neither of these systems would appear to account for the powerful augmentation in myocardial contractile force, acceleration, and peripheral vasoconstriction responsible for the profound elevations in blood pressure regularly elicited in the present experiments. The precise origin of such fibers therefore remains unknown, although it may be that the massive responses simply reflect the nonphysiologic summation of simultaneous activation of all the pressor afferents present in the trunk.

After entering the medulla oblongata, afferent cardiorespiratory fibers in the vagus pass through the tractus solitarious to relay in the tractus and its nucleus (14). Projections to the medial reticular formation or to the lemniscal system involving pressor responses are longer and more indirect (15, 16). Certainly, modulation by central nervous mechanisms above the mesencephalon are involved (17). It is clear from the present experiments that effector neurons subserving multiple types of autonomic cardiovascular activity can be reflexly recruited through these cardiopulmonary inputs.

The differential responses in contractile force in multiple myocardial segments of chronotropic and dromotropic states of the SA and AV nodes and of systemic arterial blood pressure have not been simultaneously described during the complex interaction of direct and reflex excitation of cardiorespiratory afferent and efferent mechanisms. For example, note the relatively minor suppression in SA nodal firing rate (atrial rate) of panel A (Fig. 1) concomitant with marked suppression in atrial contractile force and AV nodal blockade. Accompanying ECG tracings reveal, of course, appropriate lengthening of P–R intervals leading into dissociation of P and QRS complexes. Such simultaneous recordings reveal highly selective effector responses within the heart. Further, suppression in contractile force is considerably greater in the right ventricular conus and left ventricular anterior surface than occurred simultaneously in the right ventricular sinus region. These data strongly indicate more highly restricted activation patterns via parasympathetic cardiac nerves than has been appreciated heretofore.

In contrast to the complex positive and negative inotropic and chronotropic feedbacks when the vagi are intact, stimulation of the central ends of either left or right transected vagosympathetic trunk elicited vigorous pressor responses (panels D and E, Fig. 1). In a larger series of dogs, Worthen and Peiss reported similar changes in heart rate and systolic pressures, with interesting differential alterations in these responses following extensive RF lesioning of hypothalamic, subthalamic, and other ventrally located thalamic structures (17).

It is well-established that the cervical vagus incorporates varying numbers of sympathetic fibers which exert direct influences

upon the heart. Thus augmentation in both pressure and contractile force, with or without cardiac acceleration, may be elicited in all four chambers of the heart during excitation of the sympathetic components of the trunk. Stimulation of the parasympathetic component elicits negative inotropic and chronotropic influences, again observed in all four chambers. There is algebraic summation of these two opposing effects during stimulation of the efferent vagosympathetic trunk (18).

Particular attention is called to the induction of atrial fibrillation as a result of reflex neural influences. While such fibrillation is relatively common as a result of direct electrical stimulation of the vagus, it is not generally associated with reflex stimulation. The severe ventricular dysrhythmias associated with it serve to further illustrate the possible importance of the nervous system in disrupting normal levels of electrical excitability within the myocardium. While such disturbances have recently been reported during electrical excitation of efferent sympathetic nerves in the dog (19) such reflex induction of cardiac dysrhythmias through the parasympathetic nerves has not been thoroughly documented.

*Summary.* Stimulation of the cervical vagosympathetic trunk may elicit either inhibitory or excitatory responses in the heart, or a combination of both, depending upon the varying content of parasympathetic, sympathetic, and afferent nerve fibers. Visceral afferent fibers contribute importantly to reflex feedbacks to the heart, as well as to recruitment of peripheral circulatory and neurohumoral mechanisms of cardiovascular control. Profound pressor responses may be elicited by excitation of afferent fibers within the cervical vagosympathetic trunk.

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