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NEURAL CONTROL OF THE HEART

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The Heart as a Sensory Organ

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Three groups of receptors in the heart are activated by changes in pressure in the cardiac chambers. Those at the venous-atrial junctions with myelinated vagal afferent nerves indicate changes in heart rate and degree of atrial filling. A second group, present in all the cardiac chambers, served by unmyelinated vagal afferent nerves, signals changes in ventricular preload, afterload and cardiac contractility. A third group, also present in all the cardiac chambers, has both myelinated and unmyelinated afferent nerves that pass to the spinal cord. Their normal function is unknown. Abnormal activation of the cardiac mechanoreceptors during myocardial ischemia may be important in the genesis of life-threatening arrhythmias.

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Cardiac Receptors

There are three groups of receptors in the heart that are activated by changes in pressure in the cardiac chambers. One group has large unencapsulated endings that are clustered at the junction of the caval veins with the right atrium and the pulmonary veins with the left atrium. These cardiac receptors are served by myelinated afferent vagal nerves that conduct at velocities of 8 to 32 m/s. A second group is served by unmyelinated afferent vagal nerves (C fibers) that conduct at velocities of 2.5 m/s or less. These thin nerve fibers are part of a rich innervation throughout the myocardium, and are present in the pericardial, epicardial, interstitial and perivascular tissues (1). No specific endings, however, have been identified in this network of fibers. A third group of receptors, also present throughout the chambers of the heart, have both myelinated and unmyelinated afferent nerves that travel to the spinal cord with the sympathetic nerves, the so-called sympathetic afferent nerves (Fig. 1).

The nucleus tractus solitarius. The afferent nerves from these cardiac mechanoreceptors terminate in the nucleus tractus solitarius in the medulla oblongata. This nucleus also receives input from receptors in the lungs, the arterial baro- and chemoreceptors, receptors in the skeletal muscles, as well as from the trigeminal and vestibular nerves, the hypothalamus and the locus coerulus. The efferent fibers from this nucleus pass to the cardiac vagal nuclei in the medulla, other nuclei in the reticular formation of the brain stem and the sympathetic preganglionic nuclei in the intermediolateral horns of the spinal cord to the hypothalamus and other centers in the brain. Thus, the nucleus tractus solitarius is a vital integrating center for the reflex control of cardiac circulation (2,3).

Function of the three groups of cardiac receptors in the heart. The receptors at the venous-atrial junctions signal changes in heart rate and the degree of atrial filling. By reflexly changing the sympathetic outflow to the sinus node and thus altering heart rate, the receptors help to maintain a constant cardiac volume. They do not cause alterations in ventricular contractility. By governing the release of antidiuretic hormone from the posterior pituitary gland, they have, in conjunction with the arterial baroreceptors, a key role in regulating body water. The receptors with vagal C fiber afferent nerves respond to increased volume of the heart. Those in the ventricles signal changes in ventricular preload, afterload and cardiac contractility. At times, these receptors have periods of increased activity unaccompanied by changes in the performance of the heart. Like the arterial baroreceptors, they have a restraining influence on the vasomotor centers. However, unlike the arterial baroreceptors,

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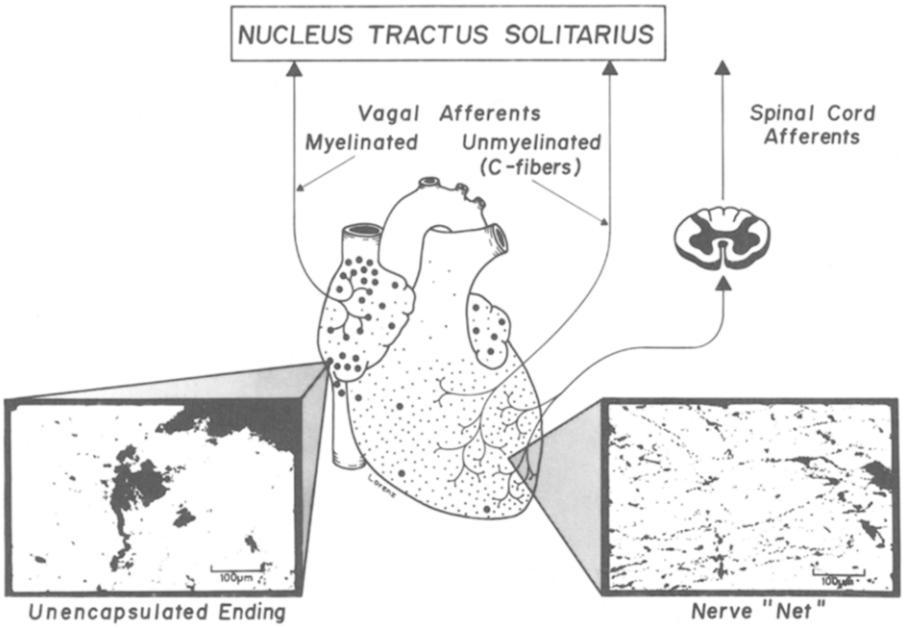


Figure 1. Mechanoreceptors in the heart and their afferent fibers. The unencapsulated endings subserved by myelinated vagal afferent nerves are localized to the venous-atrial junctions; the nerve "nets" subserved by unmyelinated vagal afferent nerves and those by spinal cord afferent nerves (sympathetic afferent nerves, myelinated and unmyelinated) are present in all the chambers of the heart.

they are not involved in the short-term regulation of arterial blood pressure. In addition, the changes in sympathetic outflow that they invoke to the various systemic vascular beds differ within species from those of the arterial baroreceptors, and there are also differences among the species. Thus, in the dog and cat, the cardiopulmonary receptors have less influence on the muscle resistance blood vessels than do the arterial baroreflexes, whereas the reverse is true in human subjects. It is likely that cardiopulmonary receptors with vagal afferent nerves, both myelinated and unmyelinated, regulate the release of renin from the kidney since both types of receptors modulate renal sympathetic nerve traffic.

The normal function of the mechanoreceptors with spinal afferent nerves is unknown. They can display a tonic impulse activity with normal cardiac dynamics. Some of the receptors may respond mainly, if not solely, to chemical stimuli such as bradykinin and lactic acid. These chemosensitive endings may be responsible for the perception of cardiac pain (4–8).

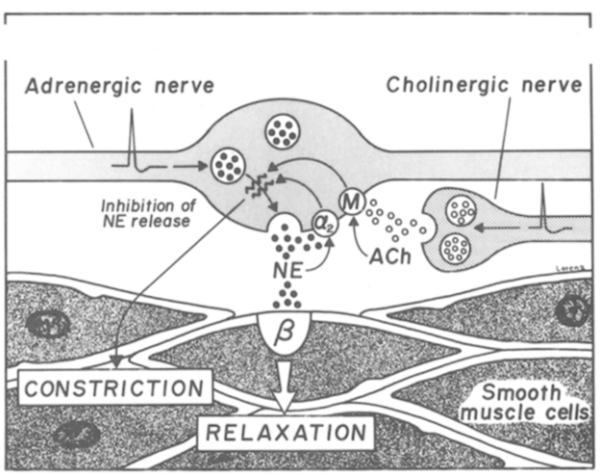
Cardiac chemoreceptors. Cells with the histologic appearance of chemoreceptors have a blood supply from a proximal coronary artery. These cells are activated by serotonin (5-hydroxytryptamine) and this causes an increase in arterial blood pressure. In contrast, serotonin injected more distally causes a decrease in pressure (Bezold-Jarsch reflex) (9).

Abnormal Activation of Sensory Endings in the Heart

Spasm of the coronary arteries is now considered one of the common causes of sudden death. The hemodynamic consequences of the spasm are due not only to diminished function of the ventricular muscle, but also to activation of sensory receptors in the heart. It is the latter that is important in the genesis of the cardiac arrhythmias.

Mechanisms for coronary vasospasm. Although the occurrence of coronary vasospasm and its consequences have been documented, the mechanisms responsible have not been elucidated. Recently, it has been demonstrated (10) in isolated canine coronary arteries that beta-adrenoceptors predominate, and that the norepinephrine released by sympathetic nerve activation leads to relaxation of these vessels. This provides an explanation for the clinical observation

Figure 2. Coronary neuroeffector junction. Interaction of cholinergic and adrenergic nerves. The acetylcholine (ACh) (**open dots**) released when the cholinergic nerves are activated acts on muscarinic receptors (M) on the sympathetic nerves to reduce the output of norepinephrine (NE) (**closed dots**). Since less norepinephrine is then available to activate the beta-adrenoceptors (β), the degree of relaxation of the smooth muscle is reduced.



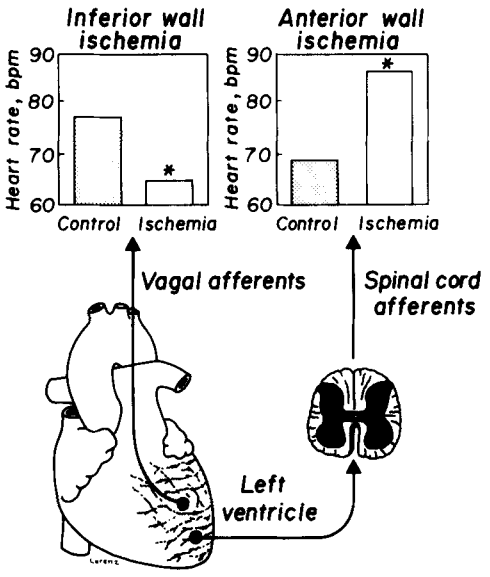


Figure 3. Afferent innervation of the heart. When infarction of the left ventricle occurs, sensory endings are activated and cause hemodynamic changes. If the ischemia involves mainly the posteroinferior part of the ventricle, where the majority of the endings of unmyelinated vagal afferent fibers are found, there is a reflex bradycardia and hypotension. If the ischemia involves the anterior wall of the left ventricle, tachycardia and hypertension may ensue. * = significant difference from control. (Bar graphs based on data from Perez-Gomez et al. [21] with permission.)

(11) that beta-adrenoceptor antagonists can aggravate coronary vasospasm. The coronary vessels also have a cholinergic nerve supply. These nerves, when active, release acetylcholine; this acts on muscarinic receptors on the sympathetic nerve terminals to reduce the output of norepinephrine and, hence, less adrenergic transmitter is available to cause relaxation of the coronary smooth muscle (Fig. 2) (12). This explains the finding (13) that muscarinic agonists can precipatate coronary spasm in human beings.

Endothelium and platelet aggregation. In normal circumstances, the endothelium, which produces prostacyclin, has a key role in preventing aggregation of platelets. At atheromatous plaques, the amount of prostacyclin generated

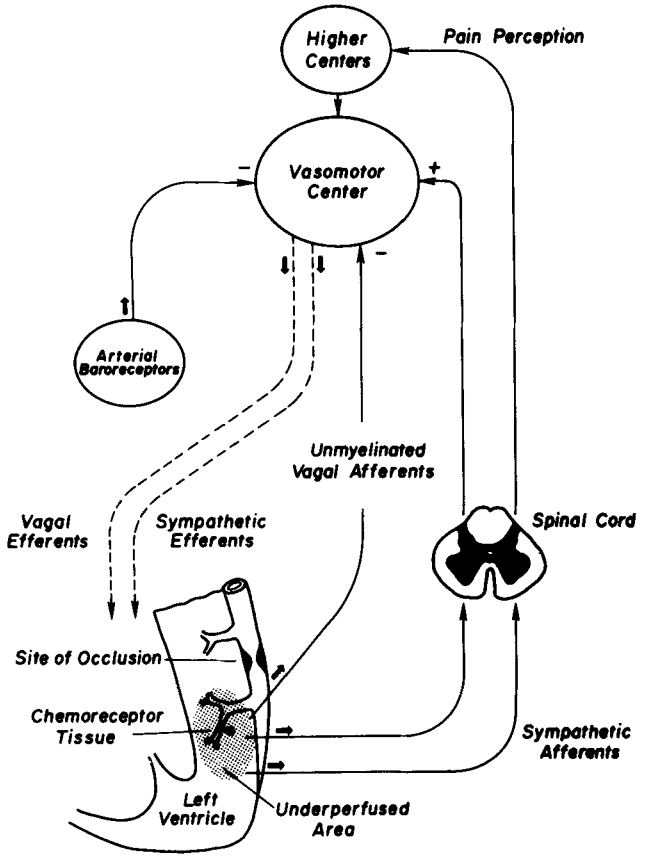
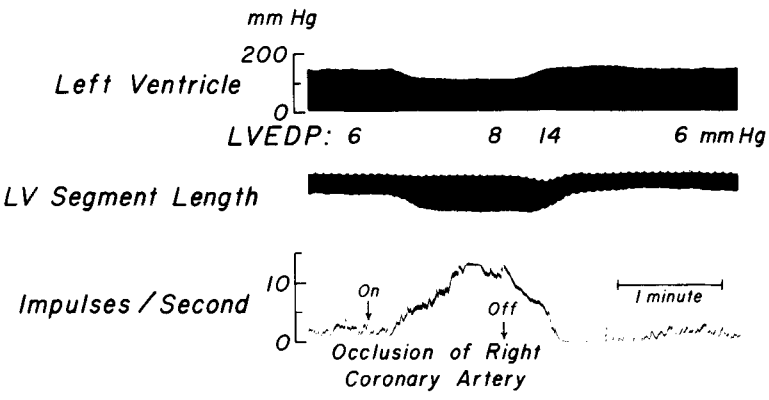


Figure 5. Reflex effects of coronary occlusion which may lead to ventricular arrhythmias. When the ischemic area involves both the anterior and inferior walls of the left ventricle, afferent nerves are excited which pass by unmyelinated vagal fibers to the vasomotor center and depress it. Simultaneously, afferent nerves are activated and pass to the spinal cord and then to the vasomotor center, which tends to excite it. This excitation may be reinforced by the chemoreceptor tissue, sensitive to serotonin (5-hydroxytryptamine) from aggregating platelets (9). As a consequence, instead of the usual reciprocity between the vagal and sympathetic efferent nerves to the heart, both sets of nerves may be activated. The simultaneous depression (through the vagal efferents) and excitation (through the sympathetic efferents) of the conducting tissue may cause electrical inhomogeneity of the heart muscle and set the stage for ventricular arrhythmias.

Figure 4. Left ventricular C fiber activity during occlusion of right coronary artery in the cat. Left ventricular end-diastolic pressure (LVEDP), left ventricular (LV) segment length (downward deflection means increased length) and discharge frequency in a left ventricular receptor are shown before (on) and during (off) occlusion. The receptor initially has a low rate of discharge that is greatly increased 20 seconds after onset of the coronary occlusion. During occlusion, the increased firing occurs together with the bulging of the ischemic area. The time lag between the release of occlusion and the decrease in systolic bulging was probably due to an observed vasospasm of the coronary artery, that relaxed slowly on release of the ligature. Disappearance of the dyskinesia was accompanied by a rapid decrease in discharge frequency. (Reprinted from Thorén et al. [25] with permission.)



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locally by the vessel wall may be reduced, thus favoring platelet aggregation (14). If the endothelium is normal, platelet products such as adenosine triphosphate and serotonin cause relaxation as does thrombin, of the smooth muscle by the formation of an unknown substance or substances (endothelium-mediated relaxing factors). If the endothelium is damaged, platelets aggregate, and serotonin and thromboxane A_2 act directly on the smooth muscle to cause its contraction (15,16). As a consequence, vasoconstriction is superimposed on the mechanical obstruction, and hypoxia of the involved myocardium ensues. Anoxia augments the constriction to substances released from the platelets (17) and also inhibits any normal endothelium at the site of the lesion from releasing a relaxing substance or substances (18).

Arrhythmias in myocardial ischemia and infarction. Thus, coronary vasospasm sets in motion a sequence of events that lead to myocardial ischemia and the possibility of sudden death by ventricular tachycardia or ventricular fibrillation. After cardiac denervation, the heart is protected from life-threatening arrhythmias after myocardial infarction, indicating the importance of the nerve supply in its development (19). The majority of patients have signs of autonomic disturbance during acute myocardial ischemia. Those with inferior infarction of the left ventricle often show signs of vagal overactivity including bradyarrhythmia and hypotension; those with anterior infarction have evidence of sympathetic overactivity with sinus tachycardia and hypertension (Fig. 3) (20,21). These arrhythmias and the hemodynamic consequences are in keeping with the fact that the majority of the left ventricular receptors with vagal afferent nerves are located in the posteroinferior wall of the left ventricle, whereas those with sympathetic afferent nerves are in the more anterior wall (22).

The intracardiac production of prostaglandins can activate left ventricular receptors with vagal afferent nerves, particularly in the posterior wall of the heart by stimulating chemosensitive endings; this can cause a systemic cardiovascular depressor reflex (23). Bradykinin, which is released by the ischemic heart, excites cardiac sympathetic afferent fibers. This excitation caused by bradykinin, in addition to excitation of these fibers by the changes in cardiovascular dynamics after myocardial ischemia, could evoke reflex pressor effects (24). Animal studies (25) have shown that activation of unmyelinated vagal afferent nerves from the left ventricle by the systolic bulging of the ischemic myocardium may inhibit the sympathetic outflow to the systemic circulation while increasing vagal efferent activity to the heart (Fig. 4). Activation of sympathetic afferent nerves may exert an excitatory effect on the heart and cause an increase in total systemic vascular resistance. The simultaneous activation of both the vagal and sympathetic afferent nerves could result in an increase in both vagal and sympathetic efferent activity to the heart, instead of the usual reciprocity between these two systems (Fig. 5) (26). If this occurs, it will increase the susceptibility of the patients with myocardial infarction to life-threatening arrhythmias.

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