
The Bezold-Jarisch Reflex Revisited: Clinical Implications of Inhibitory Reflexes Originating in the Heart

ALLYN L. MARK, MD

Iowa City, Iowa

The concept of depressor reflexes originating in the heart was introduced by von Bezold in 1867 and was later revived by Jarisch. The Bezold-Jarisch reflex originates in cardiac sensory receptors with nonmyelinated vagal afferent pathways. The left ventricle, particularly the inferoposterior wall, is a principal location for these sensory receptors. Stimulation of these inhibitory cardiac receptors by stretch, chemical substances or drugs increases parasympathetic activity and inhibits sympathetic activity. These effects promote reflex bradycardia, vasodilation and hypotension (Bezold-Jarisch reflex) and also modulate renin release and vasopressin secretion. Conversely, decreases in the activity of these inhibitory sensory receptors reflexly increase sympathetic activity,

vascular resistance, plasma renin activity and vasopressin.

Long regarded as pharmacologic curiosities, it is now clear that reflexes originating in these inhibitory cardiac sensory receptors are important to the pathophysiology of many cardiovascular disorders. This paper reviews the role of inhibitory cardiac sensory receptors in several clinical states including 1) bradycardia, hypotension and gastrointestinal disorders with inferoposterior myocardial ischemia and infarction, 2) bradycardia and hypotension during coronary arteriography, 3) exertional syncope in aortic stenosis, 4) vasovagal syncope, 5) neurohumoral excitation in chronic heart failure, and 6) the therapeutic effects of digitalis.

The Bezold-Jarisch reflex—an inhibitory reflex originating in cardiac sensory receptors—is a timely topic for an inaugural issue heralding advances in cardiovascular science during the last 25 years. The concept of reflexes originating in the heart was introduced more than a century ago (1). Nevertheless, in 1958 when the American College of Cardiology launched its first journal, the Bezold-Jarisch reflex was regarded as a pharmacologic curiosity. In contrast, in 1983 it is clear that inhibitory reflexes originating in the heart are important to the pathophysiology of major cardiovascular disorders. The purpose of this paper is to review the clinical implications of reflexes originating in inhibitory cardiac sensory receptors.

Reflexes originating in cardiac sensory receptors can be classified according to various characteristics: 1) location of the receptors, for example, atrial or ventricular, 2) types of afferent fibers, for example, myelinated versus nonmyelinated, 3) pathways of the afferent fibers, for example, in vagal or sympathetic nerves, 4) natural stimuli to the reflex, for example, mechanosensitive versus chemosensitive, and 5) cardiovascular effects, for example, inhibition or excitation. An exhaustive review of these features of cardiac reflexes is beyond the scope and purpose of this paper, and the interested reader is referred to several excellent reviews (2-6).

Cardiac receptors with vagal afferent pathways can be divided into those with myelinated and nonmyelinated fibers (2-4,6). The evidence indicates that cardiac receptors with nonmyelinated (C-fiber) vagal afferents are inhibitory and appear to constitute the afferent limb of the Bezold-Jarisch reflex. These receptors with C-fiber afferents appear to be heterogenous in terms of responsiveness to chemical and mechanical stimuli (2,6). Most respond to veratrum alkaloids, the classic pharmacologic stimulus for the Bezold-Jarisch reflex. The receptors do not respond directly to hypoxia and hypercapnia (7). Some respond primarily to chemical substances, others primarily to mechanical stimuli and some to both. To complicate the issue further, some drugs can sensitize or desensitize the receptors to mechanical stimuli.

From the Cardiovascular Division, Department of Internal Medicine and the Cardiovascular Center, University of Iowa College of Medicine, University of Iowa and Veterans Administration Medical Centers, Iowa City, Iowa.

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Address for reprints: Allyn L. Mark, MD, Cardiovascular Division, Department of Internal Medicine, University of Iowa Hospitals and Clinics, Iowa City, Iowa 52242.

For purposes of this review, the Bezold-Jarisch reflex is considered an inhibitory reflex originating in cardiac sensory receptors with vagal afferents which are influenced by either chemical or mechanical stimuli. Recent evidence suggests that inhibitory cardiac vagal afferents may be tonically active under physiologic conditions. Thus, either increases or decreases in activity of these afferents may contribute to circulatory derangements. Stimulation of the reflex increases parasympathetic activity and inhibits sympathetic activity, producing bradycardia, vasodilation and hypotension. Such stimulation may occur during inferoposterior myocardial infarction, coronary arteriography, exertional syncope in aortic stenosis and vasovagal syncope. Decreased activity of cardiac vagal afferent fibers enhances sympathetic activity and vascular resistance and promotes renin release and vasopressin secretion. This reduced activity may occur in cases of chronic heart failure.

Myocardial Ischemia and Infarction

The overwhelming majority of patients with acute myocardial infarction show evidence of autonomic disturbances during the first 30 to 60 minutes of the attack (8,9). Approximately 55% of the patients are reported to have bradyarrhythmias or hypotension, or both, during the early stage of infarction and 36% have sinus tachycardia or hypertension, or both. Webb et al. (9) demonstrated that the type of autonomic disturbance is related to the site of infarction or ischemia. Bradycardia or hypotension occurs much more commonly in patients with inferoposterior infarction, whereas tachycardia or hypertension occurs more commonly in patients with anterior infarction (Fig. 1). Perez-Gomez et al. (10) reviewed changes in heart rate and rhythm in patients with Prinzmetal's angina secondary to coronary artery spasm. Heart rate decreased significantly during pain in the patients with inferior ischemia, whereas it increased significantly during pain in patients with anterior ischemia. Thus, bradycardia and hypotension are more common in patients with inferoposterior ischemia and infarction.

Mechanisms. On the basis of correlation of recent experiments in animals and clinical observations in patients, we now have considerable insight into the mechanisms of these autonomic disturbances in patients with myocardial infarction. For example, during coronary occlusion in animals, the discharge of cardiac sensory receptors increases promptly (Fig. 2) (11-14). The precise stimulus to increased firing is unknown, but probably is mostly mechanical because activation occurs concurrently with systolic bulging of the ischemic myocardium. In addition, the receptors are not activated directly by hypoxia or hypercapnia (7).

Stimulation of inhibitory cardiac receptors with vagal afferent fibers during myocardial ischemia (15-26) promotes sympathetic inhibition, vasodilation, bradycardia and hypotension (the Bezold-Jarisch reflex). The physiologic

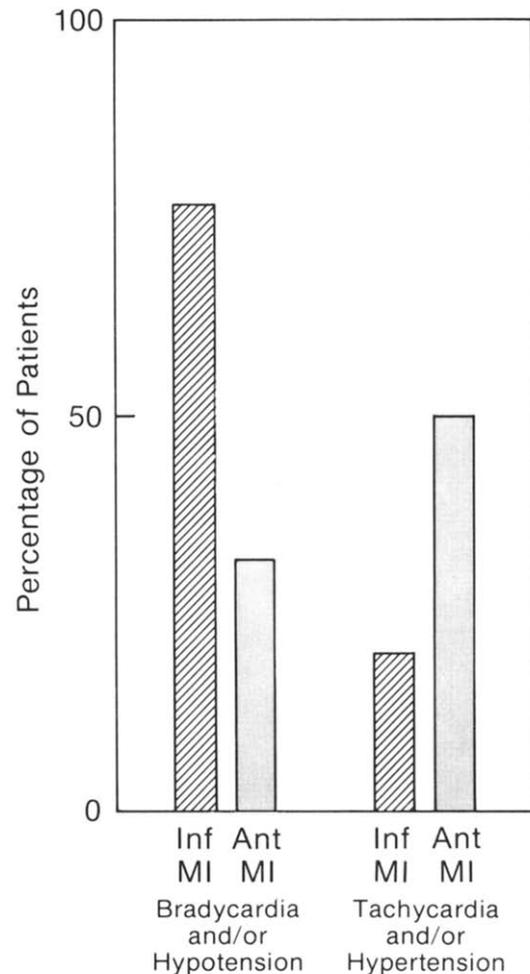


Figure 1. Comparison of the frequency of bradycardia/hypotension versus tachycardia/hypertension during the first 30 minutes of the onset of inferoposterior (Inf) versus anterior (Ant) myocardial infarction (MI). The incidence of bradycardia/hypotension was much higher in inferoposterior MI while tachycardia/hypertension was higher in anterior MI. (Adapted from Webb SA, Adegay AAJ, Pantridge JF [9], with permission.)

significance of this reflex during myocardial ischemia depends on at least four factors: 1) interaction with arterial baroreflexes, 2) engagement of various regional circulations by cardiac baroreflexes, 3) distribution of ischemia and cardiac sensory receptors, and 4) duration of the ischemia.

During systemic hypotension, arterial baroreflexes should trigger sympathetic excitation, vasoconstriction and tachycardia. However, during hypotension with accompanying myocardial ischemia, stimulation of cardiac vagal afferent fibers inhibits the arterial baroreflex (17,25,27). This has been vividly demonstrated by comparing renal vascular responses during hemorrhagic and cardiogenic shock (18,19). With comparable decreases in arterial pressure and cardiac output, renal vasoconstriction occurs much less in cardiogenic hypotension than in hemorrhagic hypotension (Fig. 3).

The sympathoinhibitory effects of cardiac vagal afferent

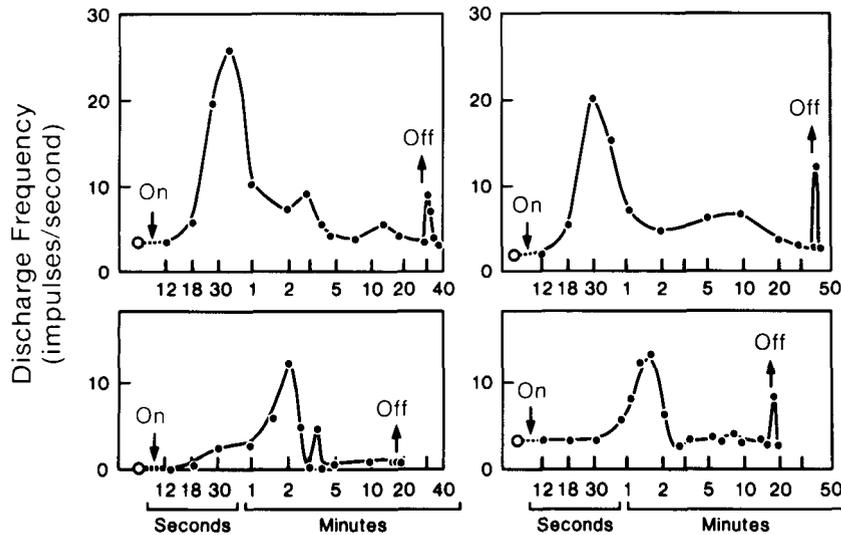
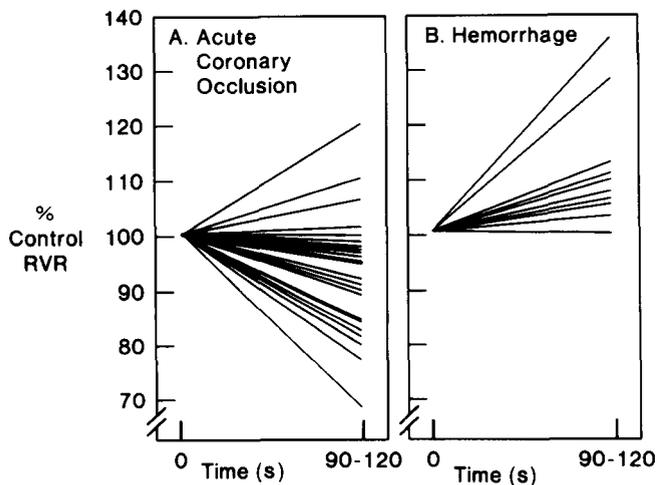


Figure 2. The discharge frequency of four left ventricular receptors with vagal C-fibers during and immediately after occlusion of the coronary artery supplying the receptor area. "On" refers to onset of coronary occlusion; "Off" refers to release of occlusion. Note 1) the prompt increase in discharge shortly after onset of occlusion, 2) the initial increase in discharge is not sustained, and 3) in three of four experiments there was a "paradoxical" increase in activity on release of occlusion. (Adapted from Thorén PN [13], with permission.)

fibers during coronary occlusion are more pronounced in the renal bed than in the limbs (22,23,26). This reflects the observation that arterial baroreceptors dominate cardiac baroreflexes in controlling sympathetic outflow to muscle, whereas cardiac baroreflexes equal or dominate arterial baroreflexes in regulating sympathetic outflow to kidney. Thus, stimulation of the Bezold-Jarisch reflex during myocardial ischemia produces particularly pronounced inhibition of renal sympathetic nerve traffic. Thames and Abboud (24) emphasized the multifaceted importance of inhibition of renal sympathetic activity during myocardial ischemia. First, it inhibits renal vasoconstrictor responses to hypotension and prevents neural release of renin and the subsequent gener-

Figure 3. Comparison of reflex renal vascular responses (RVR) to brief coronary artery occlusion (panel A) and brief hemorrhage (panel B) in the dog. Each line represents results obtained in one experiment. The protocol was designed so that both interventions produced comparable decreases in systemic arterial pressure. Despite comparable hypotension, coronary occlusion produced reflex renal vasodilation while hemorrhage produced reflex vasoconstriction. (Reprinted from Hanley HG, Raizner AE, Inglesby TV, Skinner NS, Jr [18], with permission.)



ation of the potent vasoconstrictor angiotensin. In addition, because renal nerves regulate sodium reabsorption, inhibition of renal nerve traffic could facilitate sodium and water excretion and hypovolemia.

Bradycardia and hypotension with inferoposterior infarction. The distribution of the myocardial ischemia has a strong influence on the role of the Bezold-Jarisch reflex during coronary occlusion. This relates to the concentration of inhibitory cardiac sensory receptors in the inferoposterior wall of the left ventricle (17,23,24,26). When veratridine (the classic stimulus to the Bezold-Jarisch reflex) is injected into the canine circumflex coronary artery supplying the inferoposterior wall, the reflex bradycardia and hypotension are greater than when this agent is injected into the anterior descending coronary artery supplying the anterior wall (26). In addition, reflex bradycardia, hypotension and sympathoinhibition are more common during inferior than during anterior ischemia in the dog (Fig. 4) (17,24,26). These observations indicate that the sensory endings that trigger reflex bradycardia and hypotension in response to ischemia are preferentially distributed in the inferoposterior wall of the left ventricle. It now seems virtually certain that this explains the large incidence of bradycardia and hypotension during inferoposterior ischemia and infarction in patients.

In patients, bradycardia and hypotension during inferoposterior infarction are usually transient (8,9). During coronary occlusion in cats, cardiac receptor discharge increases promptly but then usually decreases toward control values within several minutes (Fig. 2) (13). The reasons for the decrease are unknown, mainly because the precise stimulus to the receptors during ischemia is also unknown. Whatever the mechanisms, the finding that the increase in receptor discharge is not sustained during coronary occlusion may explain the clinical observation that bradycardia and hypotension are transient during inferoposterior infarction.

Coronary reperfusion. Thorén (13) observed a para-

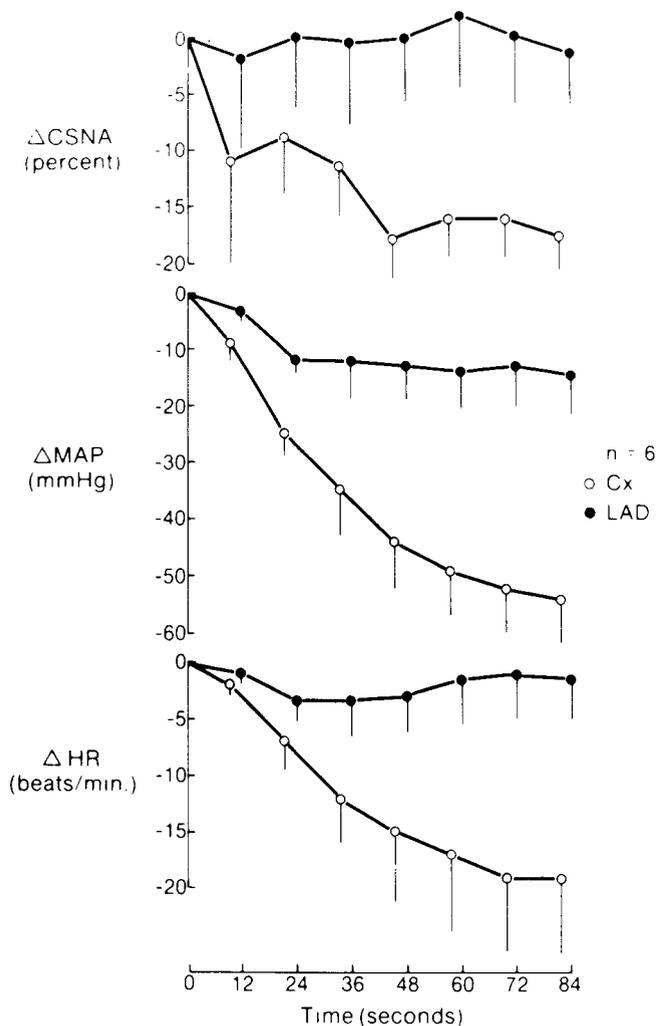


Figure 4. Comparison of changes in preganglionic cardiac sympathetic nerve activity (Δ CSNA), mean arterial pressure (Δ MAP) and heart rate (Δ HR) during circumflex occlusion (Cx) with inferoposterior ischemia versus left anterior descending occlusion (LAD) with anterior ischemia in a dog with denervated arterial baroreceptors but intact vagal afferents. Inferior ischemia produced a much more pronounced Bezold-Jarisch reflex with sympathoinhibition, hypotension and bradycardia. (Reprinted from Felder RB, Thames MD [17], by permission of the American Heart Association, Inc.)

doxical increase in receptor discharge on release of coronary occlusion and restoration of coronary blood flow in cats (Fig. 2). This was particularly prominent after prolonged coronary occlusion and persisted for as long as 2 minutes. The mechanism of reactivation of the Bezold-Jarisch reflex with reperfusion is not known, but it is of interest with regard to reperfusion of ischemic myocardium in patients. Wei et al. (28) recently examined cardiovascular reflexes during intracoronary thrombolytic therapy in patients with right versus left coronary artery occlusion. The vast majority (approximately 87%) of patients with right coronary artery reperfusion developed transient bradycardia or hypotension, or both, at the time of lysis compared with only 14% of patients with left coronary reperfusion. In patients with re-

perfusion of the left coronary artery, transient hypertension and tachycardia were more common. Patients with persistent coronary occlusion despite thrombolytic therapy had no reflex cardiovascular response. These observations appear to represent a counterpart of Thorén's observations in animals. Reperfusion stimulates the Bezold-Jarisch reflex particularly in patients with inferior myocardial ischemia.

Nausea and vomiting with inferoposterior infarction. Activation of the Bezold-Jarisch reflex may explain the large incidence of nausea and vomiting in the early stages of inferoposterior infarction. Nausea and vomiting are reported to occur in approximately 69% of patients with inferior infarction and in only 29% of patients with anterior infarction (29). Animal studies suggest that these differences in the two groups might be explained by a reflex originating in the heart (30-32) rather than by a difference in pain, analgesics, shock or heart failure. Abrahamsson and Thorén (30) demonstrated in cats that stimulation of inhibitory cardiac receptors with vagal afferent fibers by coronary occlusion produces reflex gastric dilation and retching. The gastrointestinal responses are mediated by a so-called vagal nonadrenergic, noncholinergic pathway. Johannsen et al. (31) confirmed this observation in the dog and demonstrated that the reflex gastric responses are greater during stimulation of cardiac receptors in the inferior than in the anterior wall.

Coronary Arteriography

Reflex bradycardia and hypotension. Bradycardia and hypotension occur commonly during coronary arteriography (33,34). These responses were initially attributed to direct depressant effects of contrast medium on the sinus node and myocardium, but subsequent studies demonstrated that they represent a human counterpart of the Bezold-Jarisch reflex (33-36). In 1970, Carson and Lazzara (35) reported that atropine or vagotomy prevented the bradycardia produced by coronary injections of hyperosmotic solutions in dogs. These investigators found that depressor effects of coronary arteriography result from activation of coronary stretch receptors. Eckberg et al. (33) subsequently demonstrated that atropine greatly attenuates bradycardia during coronary arteriography in patients. Thus, in both human beings and experimental animals the bradycardia during coronary arteriography results mainly from reflex parasympathetic cholinergic stimulation.

What is the location and nature of sensory receptors that trigger this reflex? Perez-Gomez and Garcia-Aguado (34) attempted to localize the site of origin by correlating the degree of bradycardia with the anatomic distribution of the coronary tree. They found that bradycardia was greatest when the angiographic medium was injected into the artery supplying the inferior wall, that is, the dominant right coronary artery (Fig. 5). In contrast, the magnitude of bra-

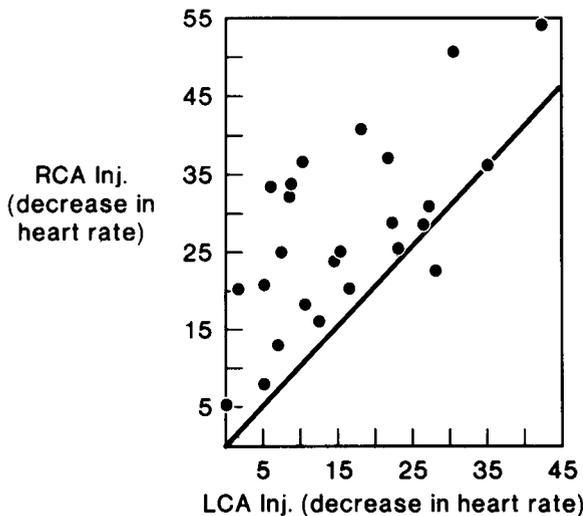


Figure 5. Comparison of decreases in sinus heart rate during right (RCA) versus left (LCA) coronary artery injections (Inj.) of contrast medium in patients with normal, obvious dominant right coronary artery circulation. Right coronary artery injections supplied the inferoposterior wall and left coronary artery injections supplied the anterolateral wall. The magnitude of the sinus slowing was greater from the right coronary injections supplying the inferoposterior wall of the left ventricle. (Reprinted from Perez-Gomez F, Garcia-Aguado A [34], with permission.)

dycardia was not influenced by the origin of the sinus or atrioventricular nodal arteries. These observations were substantiated by 12 patients who developed sinus arrest lasting longer than 2 seconds after coronary arteriography. In 85% of these patients, the contrast medium had been injected into the artery supplying the inferior wall. The vessel supplied the sinus node in only 33% of the patients. This analysis suggests that the bradycardia is predominantly reflex and originates mainly from sensory receptors in the inferior wall of the left ventricle.

One might argue that the reflex originates from distension of receptors in proximal coronary arteries and not from receptors in the myocardium, but several observations contradict this view. Injection of angiographic medium into the aortic ostium of saphenous vein bypass grafts perfusing the right coronary artery elicits pronounced bradycardia (33), indicating that the receptors are not confined to proximal coronary arteries. It also appears that the reflex is not stimulated primarily by the pressure of injection. Rapid injection of isotonic dextrose solution, which presumably increases coronary pressure, causes relatively little slowing of the heart. In contrast, slow injection of hyperosmotic angiographic medium, which probably does not increase coronary pressure, provokes considerable cardiac slowing. This suggests that the composition of the angiographic medium is more important than changes in coronary pressure for triggering the reflex (33,35).

Reflex vasodilation. Coronary arteriography elicits reflex vasodilation as well as chronotropic responses (Fig. 6) (36). The hypotension during coronary arteriography results

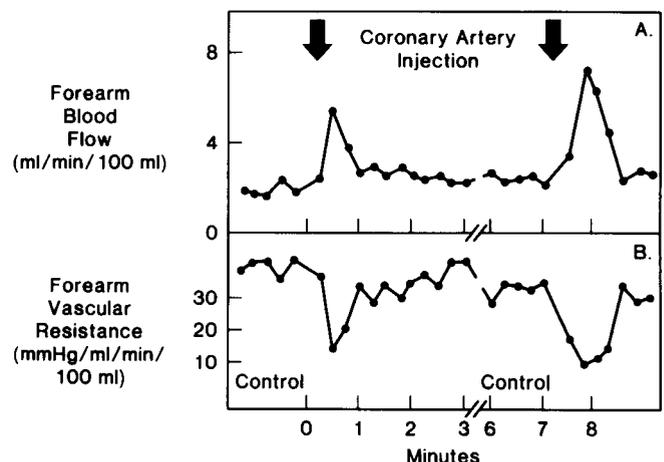
more from vasodilation than from the bradycardia because preventing the bradycardia by atrial pacing only slightly reduces the hypotension (33). Reflex vasodilation during coronary arteriography could be caused by withdrawal of adrenergic constrictor tone or activation of a sympathetic vasodilator system such as the sympathetic cholinergic pathway. The studies of Zucker and Cornish (37) in the conscious dog suggest that activation of the Bezold-Jarisch reflex triggers sympathetic cholinergic dilation in addition to withdrawal of adrenergic constrictor tone. Zelis et al. (36) found that atropine blocks reflex forearm vasodilation during coronary arteriography in human beings. White et al. (38) reported that atropine reduces the hypotension produced by coronary injections of contrast medium even when heart rate is kept constant by pacing. These findings suggest that coronary arteriography provokes reflex vasodilation in human beings at least partly by activating sympathetic cholinergic vasodilator pathways.

These observations provide a rational basis for prevention of bradycardia and hypotension during coronary arteriography. Cardiac pacing prevents bradycardia, but not vasodilation and hypotension. Atropine is more effective than cardiac pacing in preventing the hypotension because it antagonizes the reflex cholinergic vasodilation as well as the bradycardia.

Syncope

Exertional syncope in aortic stenosis. In 1935 it was proposed (39) that exertional syncope might result from hypersensitivity of carotid sinus baroreceptors or from some

Figure 6. Reflex changes in forearm blood flow (A) and forearm vascular resistance (B) produced by the injection of 8 cc of sodium and meglumine diatrizoate (Hypaque-M 75%) into the left coronary artery. Arrows indicate the time at which the injections were made. Coronary injection of contrast medium caused prompt increases in forearm blood flow and decreases in forearm vascular resistance. This vasodilation was not related to direct effects of contrast medium on forearm vessels because it was not reproduced by injections into the root of the aorta. In addition, it was blocked by atropine. (Reprinted from Zelis R, Caudill CC, Baggett K, Mason DT [36], by permission of the American Heart Association, Inc.)



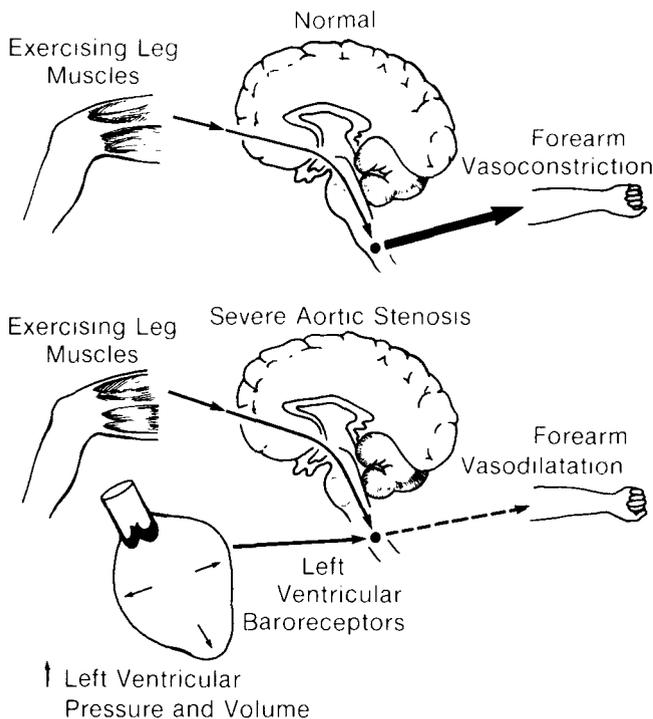


Figure 7. Schematic diagram depicting the proposed effects of activation of left ventricular baroreceptors during exercise in patients with severe aortic stenosis. As shown at the **top**, afferent impulses originating in exercising leg muscle normally produce reflex vasoconstriction in the non-exercising forearm. These studies tested the hypothesis that increases in left ventricular pressure and activation of left ventricular baroreceptors inhibit and reverse the forearm vasoconstriction. (Reprinted from Mark AL, Kioschos JM, Abboud FM, Heistad DD, Schmid PG [41], with permission.)

other "depressor reflex." Because it was soon shown that carotid sinus massage failed to produce syncope in such patients, the concept of a reflex mechanism for exertional syncope was ignored. For many years exertional syncope in aortic stenosis was attributed to an inability to increase cardiac output with exercise or to an arrhythmia despite observations that disputed these mechanisms.

Accordingly, about 10 years ago the concept of a reflex mechanism for exertional syncope was revived (40,41). It was proposed that a depressor reflex arising from stimulation of left ventricular baroreceptors might be implicated. This idea was derived from the burgeoning evidence from animal experiments that increases in left ventricular pressure and stimulation of left ventricular baroreceptors can promote reflex vasodilation and hypotension. Thus, it was suggested that in patients with severe aortic stenosis exercise increases left ventricular pressure, stimulates ventricular baroreceptors and promotes reflex vasodilation and syncope (Fig. 7).

An understanding of this hypothesis requires a brief review of the normal circulatory adjustments to exercise. During muscular exercise, sensory receptors in skeletal muscle transmit impulses to the central nervous system to initiate reflex vasoconstriction. This excitatory reflex, the somatic pressor reflex, helps to maintain arterial pressure in the

presence of the metabolic vasodilation in exercising muscle. During leg exercise, the somatic pressor reflex normally produces vasoconstriction in the resting forearm.

My colleagues and I (41) tested the hypothesis that this normal forearm vasoconstrictor response to leg exercise is inhibited or reversed in patients with severe aortic stenosis because of a depressor reflex originating in left ventricular baroreceptors. During diagnostic cardiac catheterization, forearm vascular responses to leg exercise were compared in patients with aortic stenosis and in two control groups (patients with mitral stenosis and patients without valvular heart disease). Although forearm vasoconstriction occurred during exercise in both control groups, this response was inhibited or reversed in the patients with severe aortic stenosis and a history of exertional syncope (41). Three patients with aortic stenosis and exertional syncope were restudied after aortic valve replacement. After their operation the abnormal forearm vasodilator responses to leg exercise changed to vasoconstrictor responses (Fig. 8).

This study (41) indicated that forearm vasoconstrictor responses to leg exercise are inhibited or reversed in patients with severe aortic stenosis because of stimulation of left ventricular baroreceptors. Daoud and Kelly (42) subsequently confirmed the finding that reflex vasoconstrictor responses to hemodynamic stresses are inhibited in patients with aortic stenosis.

We did not attempt to provoke syncope in our patients, but Flamm et al. (43) described sequential hemodynamic events during exercise and "near syncope" in a patient with aortic stenosis. Initially, cardiac output and arterial pressure increased and systemic vascular resistance decreased during exercise. However, with the sudden onset of near syncope, cardiac output fell to resting levels and arterial pressure decreased from 165/81 to 44/32 mm Hg without an increase in vascular resistance. Pulmonary artery wedge pressure increased. These investigators suggested that the precipitating event in exertional syncope is acute left ventricular failure but noted that vascular resistance did not increase appropriately with hypotension. Vascular resistance should increase both actively and passively during a pronounced reduction in arterial pressure initiated by ventricular failure. Thus, it is difficult to explain the failure of vascular resistance to increase during hypotension on the basis of primary left ventricular failure. More likely, the initiating event is stimulation of left ventricular baroreceptors and reflex withdrawal of vasomotor tone. Stimulation of left ventricular baroreceptors could precipitate concomitant left ventricular failure by decreasing arterial pressure and coronary perfusion or by inhibiting sympathetic drive to the heart.

Vasovagal syncope. When blood is pooled in the lower limbs during orthostatic stress (upright tilting or lower body negative pressure), arterial pressure is maintained by reflex tachycardia and vasoconstriction. These circulatory adjust-

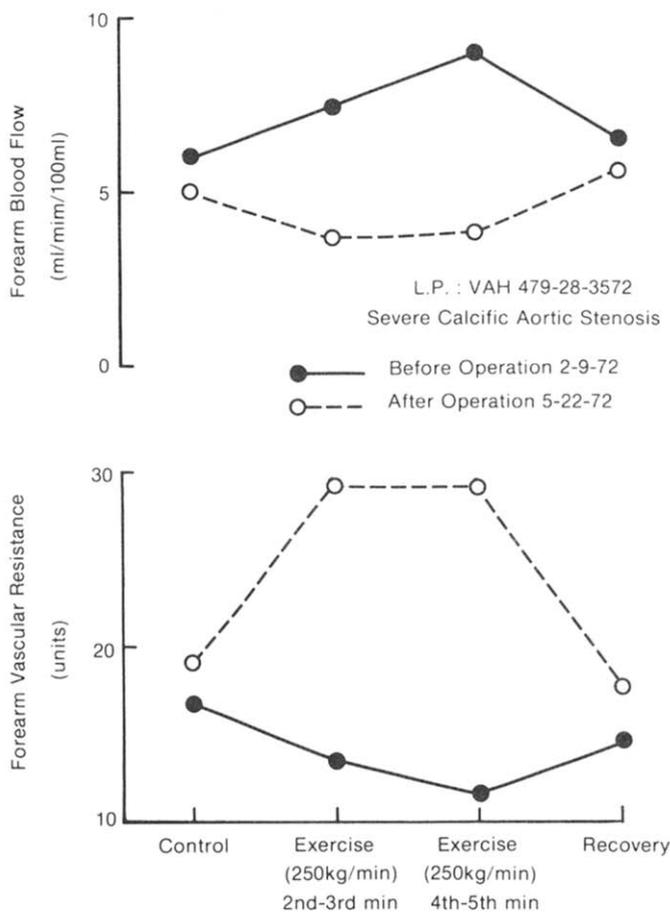


Figure 8. Forearm vascular responses to supine leg exercise in a patient with severe calcific aortic stenosis before and after aortic valve replacement. Before operation (●) the patient displayed an abnormal forearm vasodilator response to leg exercise. After operation (○) the patient displayed a normal forearm vasoconstrictor response. FBF = forearm blood flow; FVR = forearm vascular resistance. (Reprinted from Mark AL, Kioschos JM, Abboud FM, Heistad DD, Schmid PG [41], with permission.)

ments were traditionally attributed to reflexes originating in arterial baroreceptors, but studies from several laboratories indicate that cardiac baroreceptors normally play an important role in the reflex vascular responses to decreases in venous return and cardiac filling pressure (44,45). The activity of inhibitory cardiac sensory receptors normally decreases during orthostatic stress or hemorrhage because of the decrease in cardiac filling pressure. This promotes reflex sympathetic stimulation and protects against hypotension.

Although the activity of inhibitory cardiac receptors normally decreases during hemorrhage and orthostatic stress, it has been shown in animals (46) that with rapid severe hemorrhage, a vigorous contraction around an almost empty ventricular chamber can trigger an abrupt paradoxical increase in firing of inhibitory left ventricular receptors (Fig. 9). This would promote reflex bradycardia and vasodilation. A similar mechanism may explain vasovagal syncope during orthostatic stress in human beings (46,47).

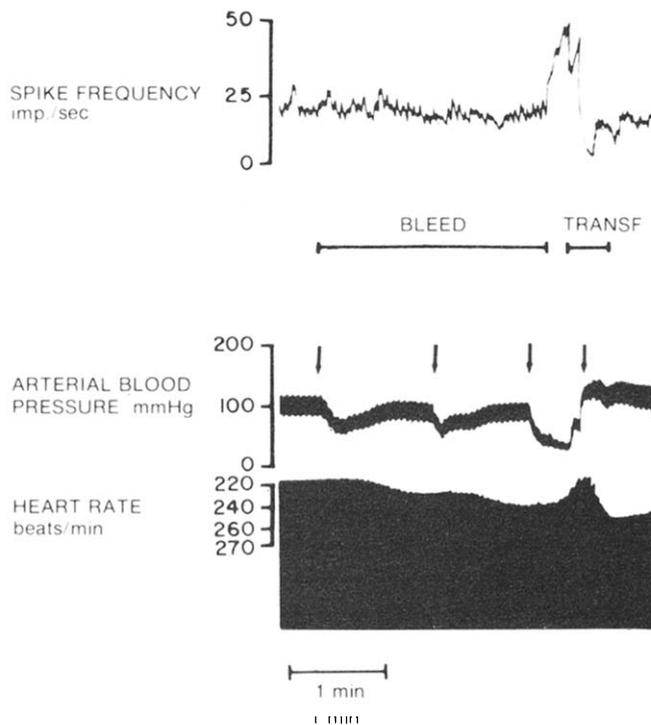


Figure 9. Effects of graded hemorrhage on the spike frequency of left ventricular receptors with nonmyelinated vagal afferents, and on arterial blood pressure and heart rate. With the initial hemorrhage (first and second arrows), there was a slight diminution in receptor discharge and tachycardia. However, with further hemorrhage (third arrow) there was a prompt, marked paradoxical increase in receptor discharge that was associated with simultaneous slowing of heart rate. With transfusion of shed blood (fourth arrow), there was instantaneous cessation of receptor activity and a simultaneous increase in heart rate. (Adapted from Öberg B, Thorén P [46], with permission.)

Heart Failure

Acute heart failure. There is evidence that the neurohumoral adjustments to heart failure and the role of cardiac receptors may vary in early and chronic heart failure (48,49). On the basis of the observations of Watkins et al. (50) in dogs, it has been proposed (48,49) that the early stage of heart failure includes a phase in which hypervolemia and increased cardiac filling pressures activate cardiac sensory endings and inhibit neurohumoral drive. Patients with acute left ventricular failure secondary to myocardial infarction showed increased glomerular filtration rate and urinary flow that returned to normal within several days or weeks (51,52). It has been speculated that this increase in renal function in patients with acute heart failure is related to increased cardiac filling pressures that stimulate cardiac sensory receptors and inhibit renal sympathetic nerve activity.

Chronic heart failure. In both animals and human beings, chronic heart failure is associated with an increased neurohumoral drive that involves increased circulating levels of norepinephrine (53,54), plasma renin activity (54), vasopressin (54) and angiotensin (55). There are exaggerated sympathoadrenal responses to exercise in chronic heart fail-

ure. Dogs with right ventricular failure exhibit a profound increase in reflex renal vasoconstrictor responses to exercise (56); patients with heart failure have exaggerated reflex forearm vasoconstrictor responses (57) and augmented increases in plasma norepinephrine (53) during exercise. Thus, there is compelling evidence for neurohumoral excitation in chronic heart failure. This increased neurohumoral drive may be related in part to impairment in arterial baroreceptor modulation of sympathetic activity and renin and vasopressin release. However, evidence also suggests that impairment in inhibitory cardiac vagal afferent fibers might contribute to increased neurohumoral drive in chronic heart failure.

Greenberg et al. (58) and Zucker et al. (59) observed a decrease in sensitivity of atrial receptors with myelinated vagal afferent fibers in dogs with chronic heart failure. This probably also pertains to ventricular receptors with non-myelinated vagal afferent fibers. The increase in atrial receptor discharge produced by increases in cardiac filling pressure was substantially reduced in dogs with low output (58) or high output (Fig. 10) (59) heart failure. This decreased sensitivity appeared to be associated with decreases in atrial compliance and degenerative changes in receptor endings (59). However, with closure of an arteriovenous shunt and regression of cardiac dilation, the sensitivity of atrial receptors was restored (Fig. 10) (60).

Zucker et al. (61) reported that dogs with heart failure do not show the normal reflex increase in urinary flow during inflation of a balloon in the left atrium. This finding supports the view that impaired sensitivity of cardiac sensory receptors may contribute to abnormalities in reflex control in heart failure.

Several studies provide evidence of abnormal cardiac baroreflex control in patients with chronic heart failure (49). Forearm vessels that normally constrict during upright tilting

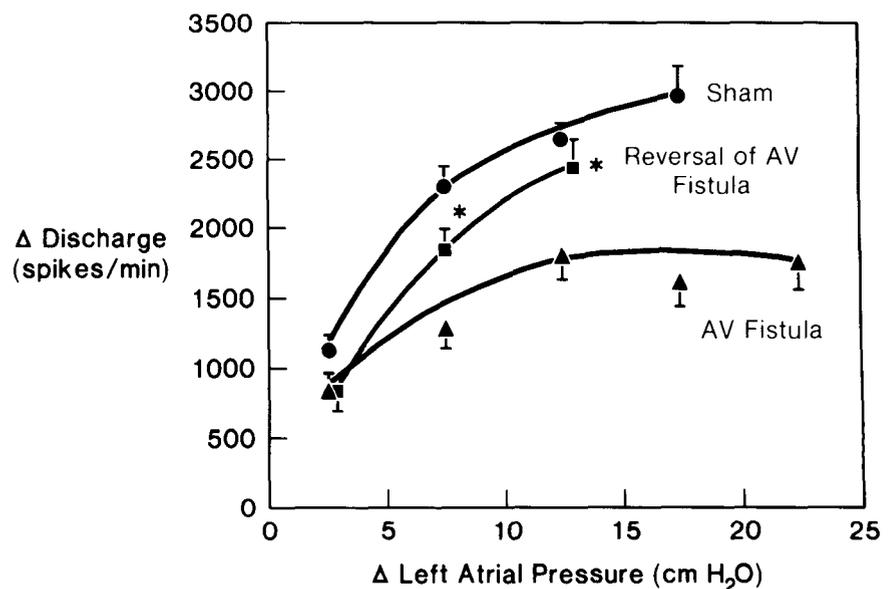
reportedly dilate during this maneuver in patients with heart failure (62). Plasma norepinephrine levels increase during standing or vasodilator therapy in normal subjects, but these levels do not increase and may even decrease in patients with heart failure (54). Although sodium restriction and diuresis increase renin activity and angiotensin levels in normal subjects, these interventions decrease renin and angiotensin in patients with heart failure (55). In addition, the upright position normally facilitates reflex vasoconstriction and the somatic pressor reflex during exercise, but in patients with heart failure standing promotes decreases in vascular resistance during exercise (49). Abboud et al. (49) interpreted these intriguing observations as evidence for impairment of cardiac afferent activity in heart failure with paradoxical restoration of activity during upright posture, sodium restriction or diuresis.

This concept has potentially profound clinical implications because it suggests that impairment in cardiac baroreflex control during heart failure is not static or irreversible, but instead may be responsive to therapeutic interventions.

Digitalis. There is evidence to suggest that digitalis may provide beneficial effects in heart failure by sensitizing cardiac baroreceptors. Digitalis has important neuroexcitatory effects (63) that may increase sympathetic nervous system activity. Cardiac glycosides administered to normal human beings increase vascular resistance (64). In contrast, Mason and Braunwald (64) demonstrated that when digitalis is given to patients with heart failure there is a decrease rather than an increase in vascular resistance. This vasodilator response may result from the inhibition of sympathetic activity produced by sensitization of cardiac and arterial baroreceptors.

Epicardial or intracoronary administration of digitalis increases the rate of firing of cardiac vagal afferent fibers (65) and thus can inhibit sympathetic nerve activity (66).

Figure 10. Changes in discharge of atrial sensory receptors in response to increases in left atrial pressure in dogs. High output failure produced by arteriovenous (AV) fistula was associated with decreased sensitivity of the atrial receptors to increased pressure. This abnormality appeared partially reversible because it returned toward control (sham animals) with closure of the fistula. (Reprinted from Zucker IH, Earle AM, Gilmore JP [60], with permission.)



More importantly, digitalis sensitizes cardiac stretch receptors to their natural stimulus (67) and thereby augments inhibition of sympathetic nerve activity produced by increases in cardiac filling pressures (68). This sensitizing effect can be seen in the absence of a change in basal discharge as well as during long-term administration of digoxin when blood levels are in the therapeutic range (69). Therefore, sensitization of inhibitory cardiac afferent fibers could importantly augment the beneficial effects of digitalis in heart failure by promoting sympathetic inhibition, vasodilation, decreases in plasma renin activity and sodium excretion.

Hypertension

There has been a resurgence of interest in the role of neurogenic factors in hypertension. Several investigators have recently studied cardiac baroreflexes in hypertension because cardiac baroreflexes are known to participate in regulation of vascular resistance, renin release, vasopressin secretion and sodium excretion (all factors implicated in hypertensive states).

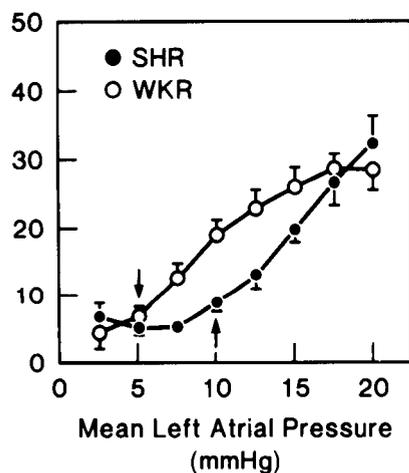
Experimental hypertension. In renal hypertensive dogs (70) and spontaneously hypertensive rats (71), there is resetting of cardiac baroreceptors to a higher pressure threshold (Fig. 11). Additionally, in spontaneously hypertensive rats the slope of the curve relating increases in left atrial pressure to inhibition of renal nerve activity is decreased slightly (Fig. 11). The mechanisms of these changes are not clear, but may be associated with altered distensibility of the heart in hypertension or to changes in baroreceptor properties.

Because of the resetting and slight decrease in sensitivity, one might expect decreased inhibition of sympathetic nerve activity by cardiac receptors in spontaneously hypertensive rats. However, the inhibitory influence of cardiac receptors is actually increased in these rats (71,72). The mechanisms of this paradoxical finding have been elucidated by Ricksten and Thorén and their colleagues (72,73). These investigators found that left atrial pressure at rest and the increase in atrial pressure with volume expansion are greater in hypertensive rats than in normotensive rats as a result of decreased distensibility or compliance of the peripheral venous system (73). Because of the higher cardiac filling pressure, the inhibitory influence of cardiac baroreceptors on sympathetic nerve activity is augmented in spontaneously hypertensive rats, particularly during volume loading.

A second mechanism that might produce augmented cardiac baroreflex control in hypertension is impairment in the inhibitory input from arterial baroreflexes. Both short- and long-term experiments in animals indicate that the inhibitory or buffering influence of cardiac baroreceptors is heightened when the inhibitory input from arterial baroreceptors is reduced, as may occur in systemic hypertension (15,74).

Human hypertension. Augmentation of cardiac baroreflexes has been demonstrated in two studies of hypertensive patients. In my laboratory (75), we examined cardiac and carotid baroreflex control of forearm vascular resistance in borderline or mildly hypertensive young men. Lower body negative pressure at -5 to -20 mm Hg was induced to reduce cardiac baroreceptor activity. Neck pressure at $+10$ and $+20$ mm Hg was used to reduce carotid baroreceptor input. Forearm vasoconstrictor responses to lower body negative pressure were greater in hypertensive subjects than in normotensive subjects (Fig. 12). Conversely, forearm

Left Atrial Receptor Activity (spikes/s)



Renal Sympathetic Nerve Activity (% of Control)

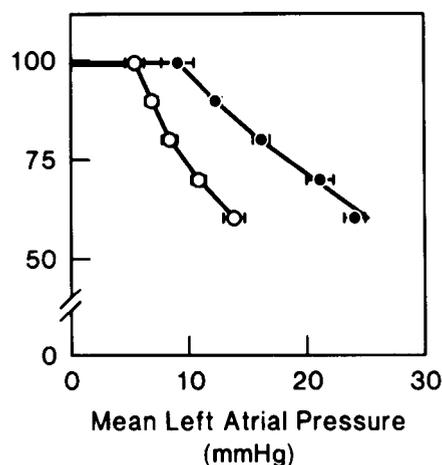
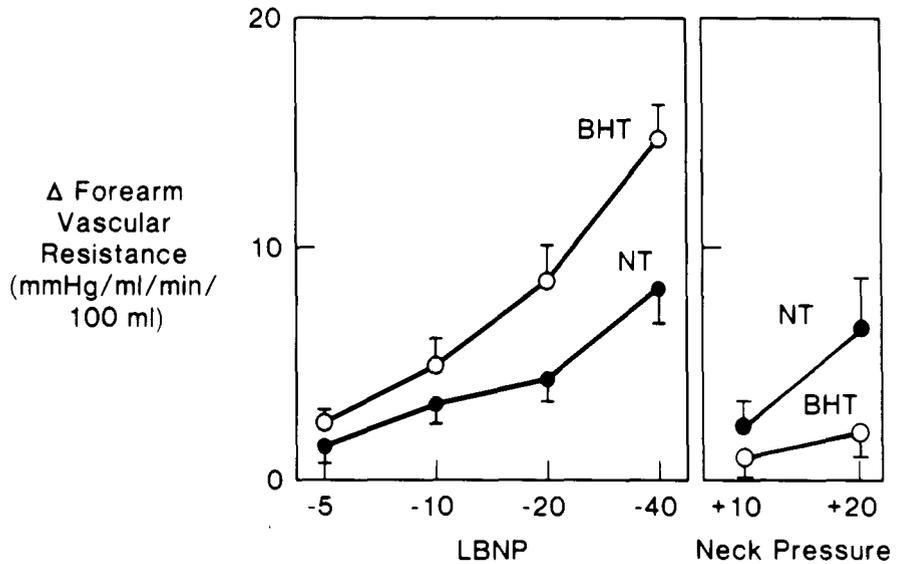


Figure 11. Abnormalities in cardiac sensory receptor function in spontaneously hypertensive rats compared with function in normotensive Wistar-Kyoto rats. The **left panel** shows resetting of the threshold for left atrial receptor activity to a higher pressure in spontaneously hypertensive rats than in Wistar-Kyoto rats (10.2 versus 4.6 mm Hg). The **right panel** shows the threshold and sensitivity for cardiac vagal afferent inhibition of renal sympathetic nerve activity during increases in left atrial pressure. The threshold was higher in spontaneously hypertensive rats than in Wistar-Kyoto rats (9.2 versus 5.4 mm Hg), and the slope of the curve relating atrial pressure to inhibition of sympathetic nerve activity tended to be flatter in spontaneously hypertensive rats. (Reprinted with permission from Ricksten S-E, Norellon E, Thorén P. *Acta Physiol Scand* 1979;106:17-22 and Thorén P, Norellon E, Ricksten S-E. *Acta Physiol Scand* 1979;107:13-8.)

Figure 12. Forearm vascular responses to lower body negative pressure (LBNP) and neck pressure in patients with borderline hypertension (BHT) and normotensive subjects (NT). Forearm vasoconstrictor responses to lower body negative pressure were augmented whereas forearm vasoconstrictor responses to neck pressure were impaired in the hypertensive subjects. This finding supports the view that cardiopulmonary baroreflexes are augmented and carotid baroreflexes are impaired in young men with borderline hypertension. (Reprinted from Mark AL, Kerber RE [75], with permission.)



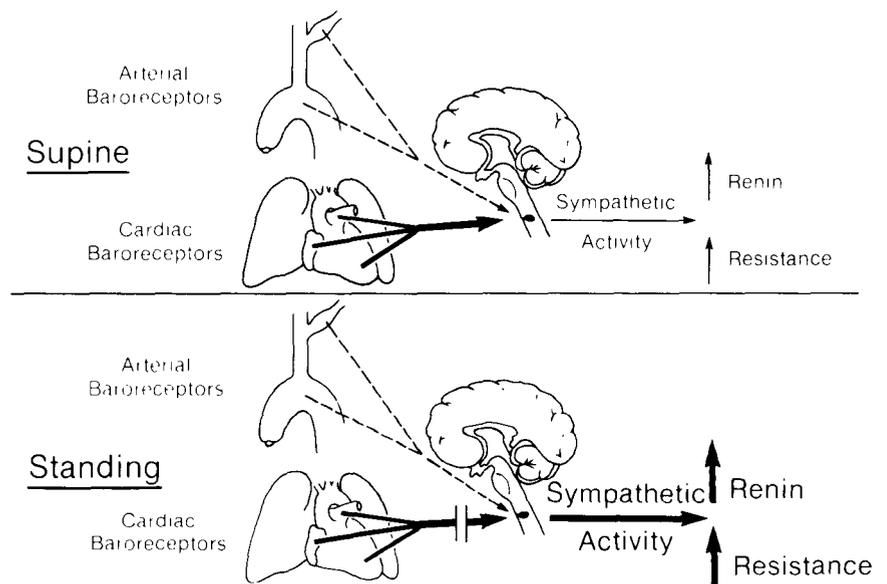
vasoconstrictor responses to neck pressure were less in the hypertensive subjects. Bevegård et al. (76) reported similar findings in a group of moderately hypertensive men: augmented forearm responses to lower body negative pressure at -20 mm Hg and a contrasting decrease in carotid baroreflex control of arterial pressure during neck pressure.

What is the mechanism of augmented cardiac baroreflexes in hypertensive patients? Peripheral venous distensibility decreases in hypertensive patients as it does in spontaneously hypertensive rats (77). Cardiac filling pressure tends to be higher in mildly hypertensive men than in normotensive subjects (75). An increase in cardiac filling pressure could increase cardiac baroreflex activity, but this is probably not the major mechanism of augmented cardiac

baroreflexes in hypertensive subjects. The slope relating forearm resistance and cardiac filling pressure was heightened in the hypertensive young men, and this slope should not be altered by changes in peripheral venous distensibility and cardiac filling pressure. It is more likely that the observations in the hypertensive men represent a counterpart of the animal experiments; that is, the inhibitory influence of cardiac receptors is augmented because the inhibitory influence from arterial baroreceptors is reduced.

Alterations in cardiac baroreflex control may contribute to the understanding of pathophysiology of hypertension in human beings. I cite here three possible examples. First, during orthostatic stress, patients with mild hypertension reportedly have exaggerated increases in systemic vascular

Figure 13. Schematic depiction of the pathophysiologic consequences of the proposed abnormalities in arterial and cardiopulmonary baroreflex control in subjects with borderline hypertension. Impairment in arterial baroreflex inhibition of the vasomotor centers would be expected to increase sympathetic activity and renin, but in the supine position, augmentation of cardiopulmonary baroreflex inhibition of the vasomotor center modulates the expected increases in sympathetic and renin activity. However, standing results in decreases in cardiac filling pressure that remove the augmented cardiopulmonary baroreflex inhibition and permit the impairment in arterial baroreceptor inhibition of the vasomotor center to be expressed as augmented postural increases in sympathetic and renin activity. (Modified from Mark AL, Kerber RE [75], with permission.)



resistance (78,79), urinary norepinephrine levels (80,81) and plasma renin activity (80,81). These exaggerated responses have usually been attributed to abnormalities in central neural or efferent mechanisms (79,81). They could, however, relate partly to augmented cardiac baroreflex control. In supine patients with mild hypertension, cardiac baroreflexes appear to exert an augmented buffering influence on sympathetic discharge (Fig. 13). Withdrawal of this augmented inhibitory influence during orthostatic stress might contribute to exaggerated orthostatic increases in vascular resistance and renin activity in these subjects (Fig. 13).

Second, Julius and Esler (82) reported that patients with low renin hypertension have a large central blood volume that reflects a shift of blood from the peripheral to the central capacitance system. These investigators suggest that the elevated central blood volume causes greater stretch of cardiac receptors that subsequently inhibits renin release.

Third, it has also been proposed that accentuated cardiac baroreflex inhibition of renal sympathetic nerve activity during volume loading may contribute to exaggerated natriuresis during saline loading in hypertension (83). Recent evidence that renal sympathetic nerves influence tubular sodium reabsorption supports this concept (84).

Clinical Implications

In this review, I have examined evidence for the role of inhibitory cardiac sensory receptors in pathologic states in patients. An awareness of this evidence should help the physician understand certain clinical states frequently encountered in the practice of cardiology, including bradycardia and hypotension during inferoposterior myocardial infarction and coronary arteriography as well as several types of syncope. There is also evidence that alterations in cardiac sensory receptors may contribute to disturbances in neurohumoral control of the circulation during hypertension and heart failure. In view of the important advances made in the past 25 years, further research in this field should improve the understanding and therapy of heart failure and hypertension. Future advances could include pharmacologic modulation of altered input from cardiac sensory receptors.

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