

Interaction of cardiovascular reflexes in circulatory control

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CARDIOVASCULAR REFLEXES and their role in the neurohumoral control of the circulation have been investigated extensively in recent years. Although these control mechanisms are complex, their influence on the circulation in physiological and pathological states is now better understood. Despite the importance of the autonomic nervous system in the rapid circulatory adjustments to acute cardiovascular stresses such as hemorrhage and shock, its contribution to the chronic circulatory changes that occur in pathophysiological conditions such as hypertension, heart failure, and stroke is not fully appreciated. During chronic stimulation the sensory input to the central nervous system may adapt, which would alter efferent autonomic influences on the cardiovascular system. Humoral, metabolic, and other tissue factors may counteract these neurogenic influences. Lesions of the central nervous system can also cause or reverse chronic hypertension (89, 178, 477), and the sympathetic nerves may have a trophic influence on vascular membrane properties (97) or vascular contractile proteins (56). These observations are further evidence for the importance of neurogenic mechanisms in pathophysiology. Thus the concept that the autonomic influences on the circulation are only transient is no longer tenable. Neurogenic reflex control of the circulation is important for both acute and chronic circulatory adaptation to stresses.

DETERMINANTS OF NEUROGENIC CONTROL

The determinants of neurogenic control have been reviewed in detail elsewhere (12, 211, 217, 365, 671) and are summarized below. Parasympathetic and sympathetic neurons in the medulla and spinal cord determine the autonomic activity that regulates the circulation through changes in cardiac output and vascular tone. Afferent signals from various sensors throughout the body constantly modulate output from these neurons. Factors operating at the level of the end-organ and the effector cells determine the influence of efferent autonomic activity. Thus, neurogenic control is influenced by factors that may originate 1) within the central nervous system (CNS); 2) at the level of efferent pathways, at the nerve terminal and its synapse or at the effector cells; and 3) at the level of the afferent or sensory endings where the inputs to the CNS originate.

A continuous influx of afferent neural impulses originating in the cardiovascular system, in other tissues and organs, and from other parts of the CNS impinges on neurons in the brain stem. Integrating these multiple inputs and their influence on autonomic neurons is complex but important in the moment-to-moment regulation of the circulation (5, 363, 594).

Traffic in different efferent nerves of the autonomic system is controlled selectively. Efferent impulses generated in the CNS are targeted to specific vascular beds and even specific segments of a vascular bed (219). Therefore defining reflex responses in terms of generalized pressor or depressor patterns is inadequate. Possibly, in the absence of any change in arterial pressure, significant changes in vascular resistance may occur in certain organs and modify their blood flow. Differential rather than uniform responses of the various parts of the circulation more effectively satisfy the requirements of different physiological and behavioral stimuli, such as exercise, eating, diving, or running.

During hemorrhage in humans, for example, there is an early and selective increase in splanchnic venous tone before splanchnic resistance increases (510). The resulting reduction in splanchnic capacitance causes a central shift of blood volume that increases cardiac filling pressure and output. In contrast an increase in vascular resistance of skeletal muscle is observed during lower-body negative pressure (LBNP) in humans, without a simultaneous increase in venous tone in muscle (12, 14, 15, 553). Withdrawing the influences of the tonic arterial baroreceptor reflex in animals actively constricts splanchnic but not cutaneous veins (75, 307).

The autonomic nervous system and various circulating hormones interact closely. For instance, hormone release depends on afferent sensory input from the heart (which modulates vasopressin release) and the activity in efferent sympathetic nerves (which controls renin release from kidney). Conversely these hormones may modify reflex responses through an influence on the sensory input, the autonomic neurons themselves, or the neuroeffector junction. For example, angiotensin facilitates norepinephrine release during sympathetic drive (4, 687) and reduces the reflex bradycardia during hypertension by interrupting vagal efferent activity (386). Conversely prostaglandins may reduce norepinephrine release during sympathetic stimulation (270, 271) and vasopressin may cause a vagally mediated bradycardia or augment the reflex bradycardia during elevation of arterial pressure (81).

The relative importance of neural versus metabolic factors should be appreciated in the final determination of tissue perfusion. Neural reflex adjustments in cardiac output, total vascular resistance, and venous tone are integrated to maintain arterial perfusion pressure to all organs. On the other hand the arteriolar resistance and the vascular tone of precapillary vessels determine nutritional flow; in some organs, such as

the heart or the exercising skeletal muscle, they are regulated primarily by the metabolic demands and the elaboration of vasoactive tissue factors (453). Structural changes in vascular walls may accentuate the influence of neural and humoral factors such as those seen in hypertension (13, 215). The relative contribution of neural, metabolic, and structural factors varies in different organs and in different physiological and pathophysiological states.

Recent reviews that address various aspects of the integration of circulatory control may be consulted for additional information (6, 12, 216, 293, 347, 363, 365, 428, 576, 577, 594); the reviews by Korner (363, 365), Spyer (594), and Kirchheim (347) may be particularly helpful.

This chapter is divided into five sections. The first defines reflex interactions, and the second outlines the CNS substrate for central integration and interaction of cardiovascular reflexes. This background information is preparation for the third section, which briefly describes the major individual cardiovascular reflexes, and the fourth section, which summarizes the evidence for specific interactions among cardiovascular reflexes. In the final section the potential importance of these interactions in selected pathophysiological states is considered.

DEFINITIONS

This section provides the concepts necessary for understanding the interaction of cardiovascular reflexes. First, the components of a single reflex arc are described. Then the approaches to investigating cardiovascular reflexes individually or with interacting reflexes are defined. Finally, the specific types of interactions are outlined and the factors that modify or determine integrated responses reviewed. A review of these first principles, necessary for understanding reflex interactions, follows.

Cardiovascular Reflex Arc

The basic elements in a cardiovascular reflex arc, as reviewed by Palkovits (493), include four general groups of neurons.

SENSORY NEURONS. Sensory endings in various tissues detect mechanical (stretch, deformation, or compression), physicochemical (temperature or change in cations), or biochemical metabolic [oxygen pressure (P_{O_2}), carbon dioxide pressure (P_{CO_2}), pH, bradykinin, etc.] disturbances. Impulses thus generated are transmitted to neurons. These endings are essentially dendrites to afferent neurons that have axons terminating in the CNS, generally in the medulla oblongata and particularly in the nucleus tractus solitarius (NTS) in the medulla.

CENTRAL NEURONS. These neurons are in the medulla, receive input from the sensory neurons, and send axons to the efferent cardiovascular neurons, i.e., the preganglionic vagal and sympathetic efferent neurons.

MODULATING NEURONS. The central neurons in the medulla are connected through long and short reflex arcs to other CNS neurons, which in turn modulate their discharge. These modulating neurons are present in all parts of the CNS but especially in the hypothalamus.

VAGAL AND SYMPATHETIC PREGANGLIONIC NEURONS. In the medulla and spinal cord these neurons innervate the heart and blood vessels through post-ganglionic fibers. A change in the homeostasis of the organism triggers the discharge of sensory afferents, which mediates reflex responses through autonomic nerves aimed at buffering the stimulus and restoring homeostasis.

Open-Loop Versus Closed-Loop Response

Traditionally cardiovascular reflexes have been studied through their responses to changes in sensory input from one group of sensory endings while the input from all other groups of sensory endings is eliminated or held constant. The resulting reflex response, then examined in various parts of the circulation, can be attributed specifically to excitation or inhibition of the sensory endings under investigation. Experiments of this kind have been carried out for decades and have provided important information about individual cardiovascular reflexes. In an open-loop response the stimulus to the receptors can be controlled independently of reflex circulatory adjustments. Examples of open-loop reflex responses (Fig. 1) include isolated carotid sinus (Moisejeff preparation) and central aortic nerve stimulation (nerve sectioned peripherally). The contribution of a given group of receptors to an integrated reflex response may also be assessed by opening the loop; for example, the contribution of sinoaortic baroreceptors to the integrated reflex control of renal nerve activity can be determined in part by examining the responses after sinoaortic denervation (i.e., with loop open).

In intact animals and in humans the reflex response triggered by activating one sensory input may in turn modify the magnitude of that sensory input or activate other sensory afferents that may influence the final response. Furthermore changes in the activity level of central or modulating neurons may modify the response of efferent cardiovascular neurons even if the sensory input from afferent neurons is constant. These are closed-loop responses (Fig. 1). Under normal physiological conditions and in abnormal circulatory states several groups of sensory afferents may be activated

simultaneously; the net reflex response cannot be deduced from an algebraic summation of responses to activating each group of afferents separately. In hemorrhagic shock, for example, arterial and cardiopulmonary baroreceptor reflexes as well as chemoreceptor reflexes may be activated simultaneously when patients are hypotensive, hypovolemic, hypoxic, and acidotic. The net response does not equal the sum of the responses observed when each reflex is activated alone. This nonlinear summation implies that reflexes interact. Activating somatic receptors in exercising muscle can elicit excitatory responses (i.e., hypertension and tachycardia). Inhibitory influences of stimulating sinoaortic and cardiac baroreflexes, hyperventilating, and lung inflation reflexes oppose these responses. When these opposing systems are stimulated, it is difficult to predict the net response, which depends on the integration and interaction of these multiple afferent impulses and the determination of the net changes in sympathoadrenal drive to the heart, peripheral circulation, and parasympathetic outflow to the heart.

Thus, studying responses to several simultaneously changed sensory inputs can elucidate the integrated responses in intact animals and humans in physiological and pathological states. Furthermore the relative contribution of various sensory inputs to the integrated net response may be more fully appreciated than if the isolated responses are studied separately.

Types of Interactions

SUMMATION OF SIMILAR RESPONSES. When two sensory inputs are activated simultaneously and their influence (inhibitory or excitatory) on the autonomic system is essentially the same, one of three types of responses may occur, depending on the degree of convergence of afferent impulses on central neurons.

The response to combined activation may be equal to, less than, or more than the sum of individual responses. These types of responses, depicted in Figure 2, are 1) mutual inhibition, or response to combined $AB < \text{response } A + \text{response } B$; 2) simple additive summation, or response to combined $AB = \text{response } A + \text{response } B$; and 3) mutual facilitation, or response to combined $AB > \text{response to } A + \text{response to } B$.

For example, although stimulating the carotid baroreceptors or aortic baroreceptors inhibits sympathetic neurons and excites vagal neurons, the response to their simultaneous activation may equal the simple addition of the responses seen when each one is activated separately. This would be true if carotid and aortic baroreceptor afferents were impinging on separate groups of sympathetic or vagal neurons. However, several studies indicate that the response to simultaneously activating these two sets of receptors is not always simple additive summation of their individual effects. Examples of the three possible types of interactions follow.

Mutual inhibition or redundancy in sympathetic neuron control by arterial baroreceptors. Separate and combined stimulation of aortic and carotid baroreceptors have been studied in terms of their hypotensive effects, their inhibitory influence on sympathetic nerves, and the evoked responses in the NTS after their electrical stimulation (35, 229, 255, 346, 478, 548). In these and more recent studies in our laboratory (255) the combined stimulation of the two sets of afferents yielded responses that were significantly less than the sum of responses when each afferent pathway was separately activated. Kezdi and Geller (346) reported that the inhibitory effect of combined stimulation of both carotid sinus areas was only 50%–55% greater than the response to stimulation of a single sinus, when it should have been 100% greater (if simple addition had occurred); this indicated mutual inhibi-

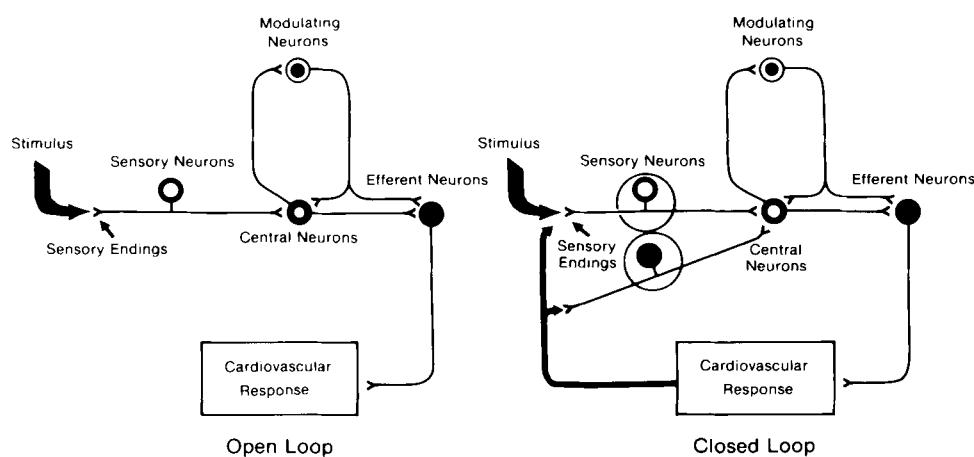


FIG. 1. Schematic of open-loop vs. closed-loop reflex responses. In latter condition, response modifies sensory input caused by a specific stimulus.

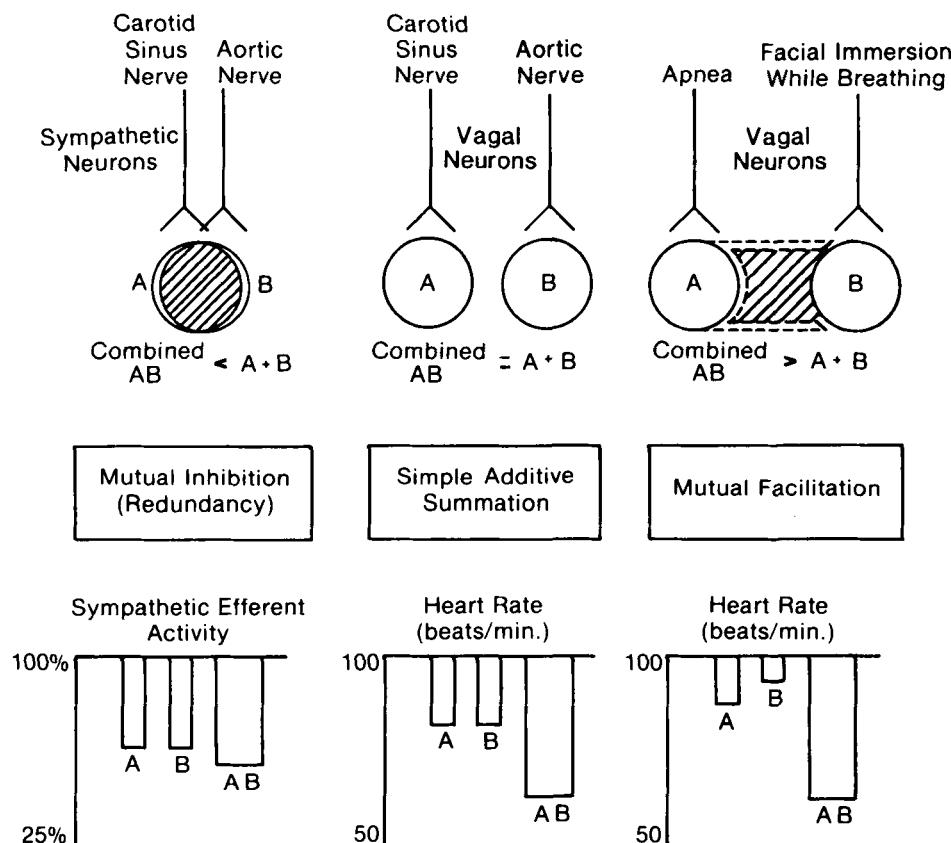


FIG. 2. Three examples of summation and interaction of reflexes causing directionally similar responses. Hypothetical patterns of afferent convergence are diagrammed with anticipated responses. Carotid sinus nerves and aortic nerves inhibit sympathetic neurons and activate vagal neurons. Apnea and facial immersion activate vagal neurons. Sympathetic neurons but not vagal neurons seem to show redundancy (see also Fig. 28).

tion. Similarly Ninomiya and Irisawa (478) show that a rise in mean aortic pressure of 50 mmHg almost completely inhibits efferent renal nerve activity when all baroreceptor afferents are intact; however, when three of the four afferents are sectioned, the remaining afferent inhibits renal nerve activity by 40% with a similar rise in pressure; stimulating the sole remaining receptor area can inhibit a relatively larger percentage of sympathetic efferents. Gabriel and Seller (229) suggest that in cats the site of interaction between the baroreceptors is the first synaptic relay for the carotid and aortic baroreceptor afferents within the NTS near the obex.

Recently we found that baroreflex-mediated vaso-dilatation in the isolated perfused hindlimb of the rabbit was similar in magnitude when the four baroreceptor nerves were intact, as when only two were present (254). Thus reflex vasodilatation with aortic baroreceptor stimulation alone or carotid baroreceptor stimulation alone was equivalent to that with a combined stimulation of both. Figure 2 shows schematically how the baroreceptor afferents may be interacting centrally. Significant overlap or redundancy in the projections of aortic and carotid sensory afferents on sympathetic neurons may lead to mutual inhibition.

Simple additive summation. In contrast to the pattern of sympathetic vascular responses, the reflex bradycardia mediated through arterial baroreflexes does not exhibit mutual inhibition, and the combined response more closely resembles an additive summation of individual responses. The reflex bradycardia seen when both aortic and carotid nerves were intact was twice that when either carotid or aortic nerves were present (254), suggesting little or no redundancy in the control of vagal neurons by aortic and carotid afferents (Fig. 2).

Mutual facilitation. The response of combined stimulation of two sets of afferents can be greater than the sum of responses to stimulation of each set separately. In humans, immersing the face in water while breathing air activates sensory endings in the face and nasopharynx and through trigeminal afferents excites vagal neurons, causing reflex bradycardia. Heistad and Wheeler (284) reported an 8% reduction in heart rate. Apnea or breath holding may cause minimal and inconsistent bradycardia averaging less than 1% (276); however, the combination of apnea and facial immersion, which provokes the diving reflex, causes marked bradycardia (avg. 23% reduction in heart rate) and in some subjects transient complete heart block (276). In

experiments on anesthetized macaque monkeys, Daly et al. (154) reported that simultaneously stimulating carotid chemoreceptors and the nasopharynx with water caused reflex bradycardia that is of much greater intensity than the summed responses of separately stimulating the chemoreceptors and the upper airways.

SUMMATION OF OPPOSITE RESPONSES. Three different combinations of responses are possible when two opposing reflexes interact (Fig. 3). One example is the inhibition of sympathetic efferent activity induced by stimulating baroreceptors with a rise in mean arterial pressure and simultaneously exciting sympathetic efferents with chemoreceptor stimulation. In Figure 3A the baroreceptor reflex is shown without any input from the chemoreceptors (solid line) and with an input from the chemoreceptors (dashed line). The added chemoreceptor stimulus has shifted the plateau of the baroreflex curve at both the low and high levels of arterial pressure upwards to an equivalent degree without changing the range or slope of the reflex efferent sympathetic activity. The threshold, range, and gain of the response have not changed. This type of interaction suggests that the control of efferent

sympathetic neurons does not overlap and that the two reflexes are operating essentially independently.

In contrast parts B and C of Figure 3 show some interaction between the two reflexes. In Figure 3B the range and slope of the baroreflex are not modified by the input from the chemoreceptors. However, the threshold of baroreceptor reflex activation is shifted as if an input from the chemoreceptor afferents is exciting sympathetic neurons and preventing the inhibitory influence of the baroreceptor afferents until the baroreceptor activity reaches a certain threshold to overcome the influence of chemoreceptors. Once this occurs the baroreflex response is not altered in any way, but the reflex now operates over a higher range of arterial pressures.

The third interaction, shown in Figure 3C, indicates that in addition to the shift in threshold of the baroreceptor reflex curve, which could be ascribed to the excitatory input from the chemoreceptors on sympathetic neurons normally controlled by baroreceptor afferents, the range and gain of the baroreflex have increased. Increase in the gain can be explained through an interaction between the two reflexes at the CNS level, whereby the baroreflex may inhibit the chemoreflex response possibly through a postjunc-

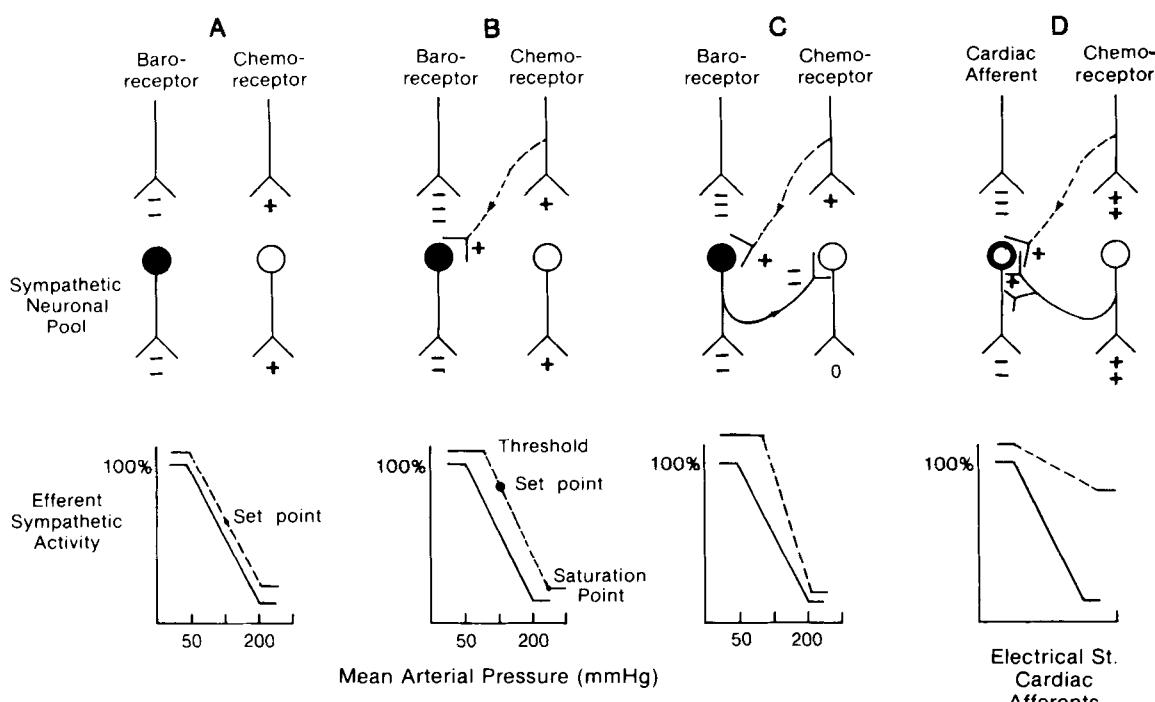


FIG. 3. Summation and interaction of reflexes causing opposite responses. Hypothetical pre- and postsynaptic interactions explain observed responses. *Solid lines*, inhibition of sympathetic efferent activity caused by activating arterial baroreceptors (A, B, C) or electrically stimulating cardiac vagal afferents (D). *Dashed lines*, influence of simultaneous stimulation of chemoreceptors. A: no change in any parameter except for simple additive shift of the baroreceptor curve upward with chemoreceptor stimulation; B: increased baroreflex threshold, but chemoreceptor stimulation changes neither gain nor range; C: increased threshold and baroreflex gain and inhibited chemoreflex at high arterial pressure. This interaction more closely represents interaction between chemoreceptors and baroreceptors with respect to renal and muscle resistances (278, 368, 673); D: cardiac reflex inhibited by stimulation of chemoreceptors with respect to muscle resistance (671, 673).

tional connection in the NTS. Thus, at high levels of baroreceptor stimulation (high arterial pressure), the chemoreceptor reflex may be totally inhibited. This latter interaction may account for our results on the interaction between chemoreceptors and arterial baroreceptors (278), where at high carotid sinus pressure the chemoreceptor reflex is markedly inhibited (Fig. 4A). We saw this interaction in terms of the vasoconstrictor influence of chemoreceptor stimulation (278) as well as the hyperventilatory response (279), further reinforcing the notion that the interaction is central. Iriki et al. (308) measured integrated renal nerve activity in rabbits during increases in mean arterial pressure and showed that adding severe arterial hypoxia increases the upper plateau level of nerve activity at low arterial pressure, shifts the threshold for inhibition of renal nerve activity with the rise in arterial pressure, and increases the gain of the baroreflex control of renal nerve activity [Fig. 4B; (365)]. Also, at high arterial pressure the excitatory effect of hypoxia on renal nerve activity was completely abolished.

The fourth interaction, shown in Figure 3D, indicates an increase in threshold and a significant decrease in the cardiac reflex gain during stimulation of chemoreceptors. Stimulating chemoreceptors inhibits

the cardiac reflex, in contrast to the arterial baroreflex, which suppresses the chemoreceptor response. These interactions are evident with respect to skeletal muscle resistance (671, 673).

SET POINT AND GAIN OF REFLEX. In a baroreflex curve the *set point* is the resting level of arterial pressure, which in a normal curve approximates the resting pressure and is generally situated along the linear portion of the curve. Increases or decreases in arterial pressure around the set point produce approximately equivalent reflex decreases or increases in heart rate or vascular resistance. If the interaction between stimuli is such that the curve shifts to the right along the pressure axis, and the threshold of the baroreflex curve is increased (e.g., Fig. 3B, C), the set point of arterial pressure is closer to the threshold so that reductions in arterial pressure may trigger reflex responses of a lesser magnitude than those elicited by increases in arterial pressure. Thus a shift of the set point on the baroreflex curve without any change in the maximal gain of the reflex may be erroneously interpreted as a change in the gain if only decreases in arterial pressure are examined. It is important to test reflex responses over a large portion of the stimulus-response relationship before making definitive conclusions about a

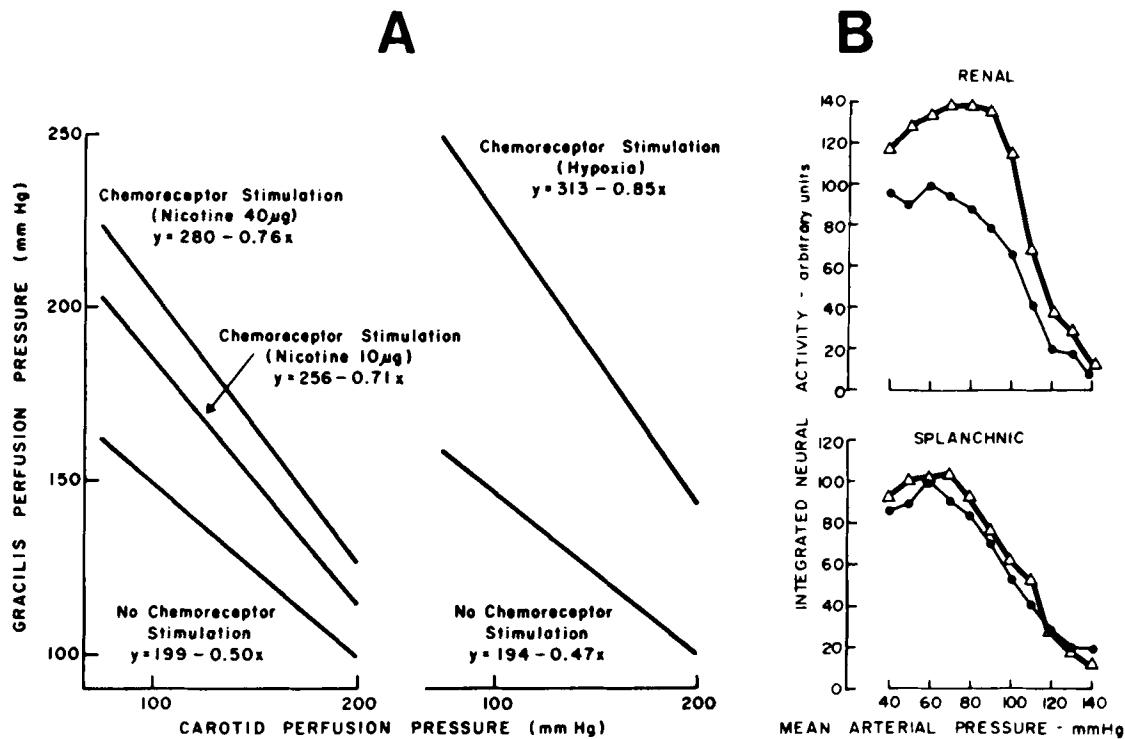


FIG. 4. A: relationship between carotid baroreceptor stimulation and gracilis perfusion pressure without and with stimulating carotid chemoreceptors in dog. Baroreflex gain is increased and the chemoreflex is suppressed at high carotid sinus pressure. B: interaction between arterial baroreceptors and chemoreceptors (systemic hypoxia) with respect to renal and splanchnic nerve activity in rabbit. Interaction with respect to the renal nerve activity is similar to that in Fig. 3C. [A from Heistad, Abboud, et al. (278) by copyright permission of the American Society for Clinical Investigation; B from Körner (365).]

change in the gain of any reflex. The study by Mancia et al. (425) reemphasizes the influence of a shift in the set point on the baroreflex curve obtained during changes of carotid sinus distending pressure in humans. These investigators found that in normotensive humans a carotid distension by neck suction causes reflex hypotension, which is of a lesser magnitude than the reflex hypertension seen during neck compression, suggesting that the carotid baroreceptors are closer to their saturation point, or maximal stretch, in normal subjects. In contrast, in hypertensive individuals, neck suction produced a much greater hypotension and neck compression produced a much lesser hypertension, suggesting that the set point is closer to threshold on the baroreflex curve of hypertensives (Fig. 5).

EFFECTOR RESPONSIVENESS VERSUS NEURAL INTERACTIONS. A potential pitfall in interpreting an interaction between two cardiovascular reflexes is the effect of a change in the base-line measurement on the response magnitude. If, for example, one reflex increases sympathetic tone and raises base-line vascular resistance and adding a second reflex, which ordinarily causes a 50% increase in resistance, now causes a 100% increase in resistance, a facilitatory interaction could have occurred. On the other hand it is important to exclude the possibility that the augmented response to the second reflex resulted simply from a nonlinear and steeper relationship between sympathetic stimulation and vascular resistance at higher basal levels of sympathetic drive. In other words the same stimulus may be applied to two different parts of the stimulus-response curve and, depending on the slope of the curve in that part, cause a greater or lesser response. For example, after partial baroreceptor denervation the baroreflex response to stimulating or unloading one set of baroreceptors is almost as large as that caused by stimulating aortic and carotid afferents in

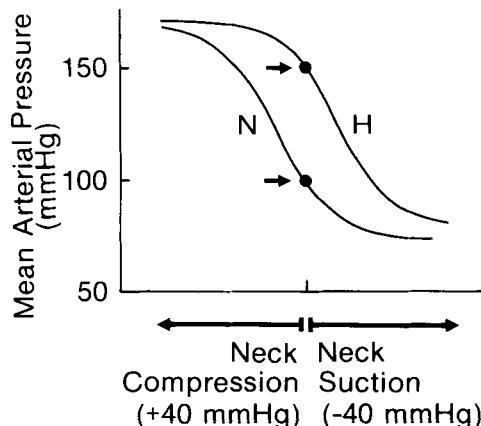


FIG. 5. Influence of changes in carotid transmural pressure on reflex changes in arterial pressure in normotensive (N) and hypertensive (H) subjects. Curve H shifts to right, and the set point (arrow) is closer to threshold transmural pressure than on curve N, which may account for reported differences in responses to carotid distension and compression in H vs. N subjects. [Adapted from Mancia et al. (425).]

combination. Before concluding that the response to stimulation of only one baroreceptor afferent is augmented because of a neural interaction, one has to rule out the possibility that increased resting sympathetic drive and resting vasoconstrictor tone resulting from partial arterial baroreceptor denervation augmented the response of the vascular bed to the same change in sympathetic drive. Figure 6 shows that in six rabbits the sectioned lumbar sympathetic chain was stimulated either at low frequencies (mean = 1.5 ± 0.3 Hz), resulting in a perfusion pressure of 84 ± 4 mmHg, or at a higher frequency (mean = 4 ± 0.5 Hz), resulting in a perfusion pressure of 111 ± 6 mmHg. These values of perfusion pressures were comparable to those observed with intact baroreceptor afferents and with one set of sectioned afferents (aortic or carotid), respectively. The results indicate that for a given increase or decrease in frequency of stimulation, the change in vascular resistance at high basal vascular resistance was comparable to or less than at low basal resistance. Thus an increase in base-line sympathetic tone, within the range in these experiments, does not cause greater vasoconstriction or vasodilatation in response to a given increase or decrease in sympathetic activity and could not account for the preservation of the baroreflex responses during activation of only one remaining set of arterial baroreceptor afferents after the other set is denervated.

We also found that reflex vasoconstrictor responses to somatic afferent stimulation were greater in the perfused *musculus gracilis* when carotid sinus pressure was low (75 mmHg) than when carotid sinus pressure was elevated to 175 mmHg (5, 16), suggesting a neural interaction between the arterial baroreflex and the somatic reflex. On the other hand changing carotid sinus pressure and resting vascular tone in the muscle

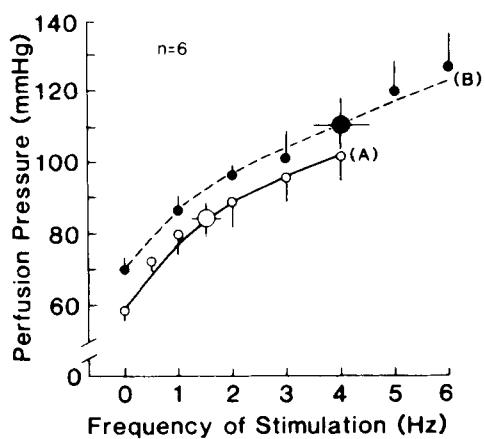


FIG. 6. Changes in hindlimb perfusion pressure (mean \pm SE) with changes in frequency of stimulation of lumbar sympathetic nerves in rabbits. Stimulation varied around a low base-line frequency averaging 1.5 Hz (curve A) and a high base-line frequency averaging 4 Hz (curve B). Slope of resistance change for a similar change in frequency of stimulation was the same or less in curve B than in curve A. [From Guo, Thames, and Abboud (255), by permission of the American Heart Association.]

may alter the reactivity of the vascular bed in response to the neurotransmitter norepinephrine. Low carotid sinus pressure tended to cause lower reflex responses to intra-arterial injections of norepinephrine into the musculus gracilis, whereas stimulating somatic afferents augmented them. Thus an augmented somatic reflex at low carotid sinus pressure could not be ascribed to an altered vascular reactivity to norepinephrine (Fig. 7). In both of these examples measurements of sympathetic efferent activity precluded a misinterpretation of vascular responses.

CENTRAL NERVOUS SYSTEM SUBSTRATE

The uncommitted heading of this section indicates our limited understanding, with few exceptions, of the specific loci for the central integration of cardiovascular reflexes. Several recent reviews have summarized in detail the many CNS circuits and relay stations that may be important in integrating cardiovascular reflexes, and more detailed analysis can be found in other reviews (347, 363, 365, 493, 594). Because interactions among reflexes may occur at one or several of these loci, we briefly summarize the evidence that supports this view as an introduction to the discussion that follows. We focus first on the medullary neurons and their connections, then on the hypothal-

amus and other suprabulbar regions, and finally on the spinal cord.

We are just beginning to understand the central neural basis for integration of cardiovascular reflexes and so cannot clearly define the subject. Many observations are important enough to be included in this review, however. Although the relationship among these observations is not clear at this point, they indicate the enormous complexity of this area. Many different neurophysiological, neuropharmacological, and neuroanatomical techniques are necessary to study integrative mechanisms. We hope this section will add an awareness of and respect for the complexity of the central integration of cardiovascular reflexes.

Medullary Nuclei

The medulla contains the major groups of excitatory and inhibitory neurons in what are traditionally referred to as the *pressor* and *depressor* regions (Fig. 8C). The pressor region is in the lateral area of the medulla, whereas the depressor region is more medial, encompassing the medial reticular formation. The excitatory pathways descend in the dorsolateral part of the lateral funiculus in the spinal cord, and the inhibitory pathways descend in the dorsolateral and ventrolateral funiculi terminating near the preganglionic sympathetic neurons in the intermediolateral horn of the spinal cord.

MEDULLARY INHIBITORY (DEPRESSOR) REGIONS. These regions either activate parasympathetic or inhibit sympathetic efferent pathways. Cardiac vagal neurons in the nucleus ambiguus and the dorsal motor nucleus activate inhibitory cholinergic vagal efferent pathways to the heart. Descending pathways from the ventromedial reticular formation with its paramedian reticular nucleus travel in the ventral funiculus and tonically inhibit sympathetic preganglionic neurons in the intermediolateral horn. Raphe nuclei in the medulla near the midline have descending serotonergic pathways in the dorsolateral funiculus that may inhibit preganglionic sympathetic neurons in the intermediolateral horn. Although the lateral reticular nucleus is excitatory, a group of noradrenergic neurons in its ventral part have inhibitory pathways to the cells of the intermediolateral horn. These neurons are referred to as the A1 group in contrast to the A2 group of noradrenergic neurons located in the dorsal part of the medulla in close proximity to the NTS and the dorsal vagal nucleus. Inhibitory pathways to preganglionic sympathetic neurons descend in the dorsolateral funiculus.

The NTS is important in integration because of its multiple afferent connections (Fig. 9). Its major efferent pathways inhibit cardiovascular responses by 1) activating vagal neurons in the nucleus ambiguus or dorsal motor nucleus; 2) activating inhibitory neurons

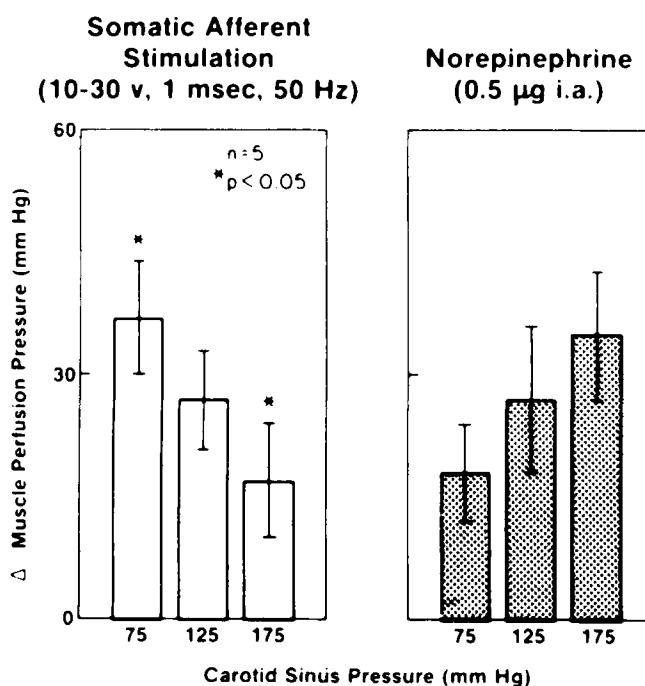
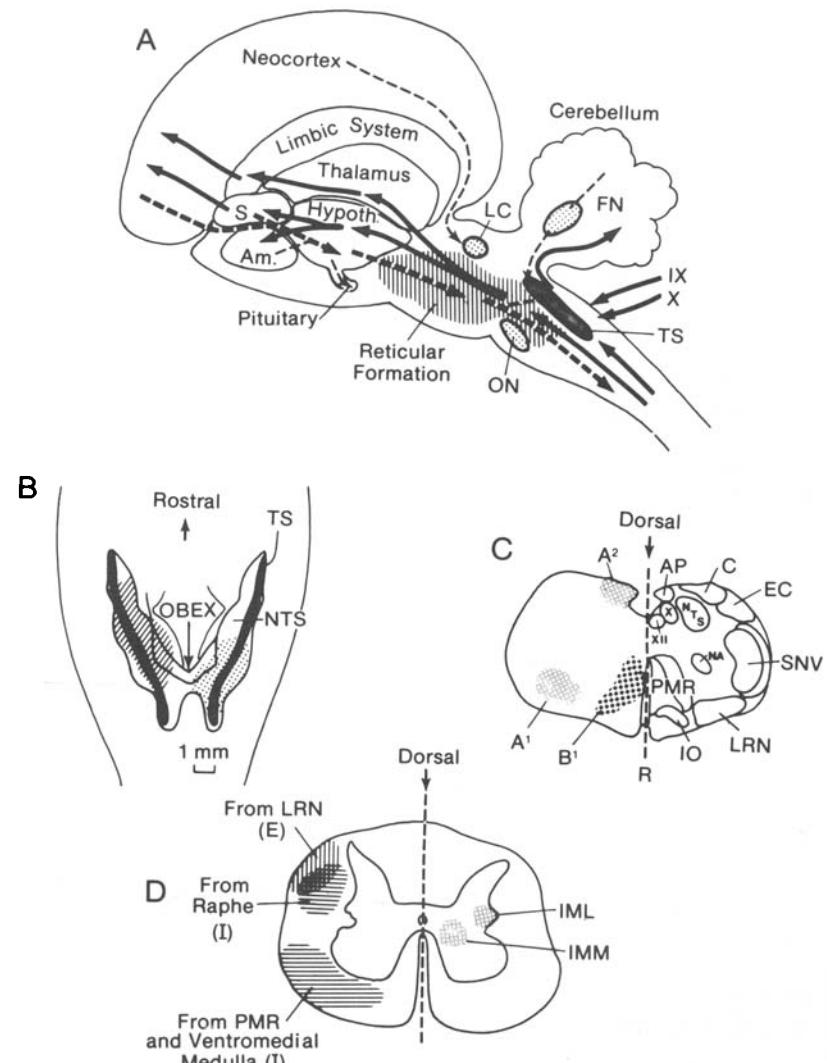


FIG. 7. Comparison of reflex increases in gracilis muscle perfusion pressure (mean \pm SE) during stimulation of somatic afferents (left panel) and intra-arterial norepinephrine (right panel) at levels of carotid sinus pressure (75, 125, and 175 mmHg). Decreased reactivity to norepinephrine did not suppress somatic reflex at high carotid sinus pressure. [From Abboud, Mark, and Thames (16), by permission of the American Heart Association.]

FIG. 8. Distribution of major excitatory and inhibitory nuclei and pathways in medulla (A, B, C), suprabulbar regions (A), and spinal cord (D). A: bulbar and suprabulbar regions. Solid lines, ascending pathways to reticulobulbar formation and then to hypothalamus (Hypoth), septum (S), amygdala (Am), and neocortex; to the thalamus, limbic system, and neocortex; and to cerebellum. Descending pathways (dashed lines) may originate in neocortex, limbic system, hypothalamus, or cerebellum [fastigial nucleus (FN)]. LC, locus ceruleus; ON, olivary nucleus; TS, tractus solitarius; IX and X, carotid sinus and vagal afferents, respectively. B: dorsal surface of medulla. Nucleus tractus solitarius (NTS) and TS projected onto dorsal surface of medulla and floor of 4th ventricle. Carotid sinus nerve afferents, carotid baroreceptors, and glossopharyngeal nerve (dashed area) and aortic nerve afferents and vagus nerve (dotted area) centrally projected. C: transverse section of medulla near obex. Note major cardiovascular nuclei and areas of noradrenergic and serotonergic (B2) neurons. Neurons containing catecholamines, dopamine, or serotonin are distributed in groups throughout central nervous system (CNS). A1 and A2, medullary noradrenergic groups connected to bulbospinal tracts that regulate cardiovascular function. A1 group is inhibitory. A2 neurons innervate NTS; their destruction causes hypertension. Locus ceruleus, another major catecholaminergic group of neurons is more rostral in dorsomedial medulla. B1 neurons are predominantly in and around raphe nuclei (R) in medulla and midbrain. Serotonergic bulbospinal tract may regulate pre-ganglionic sympathetic neurons or inhibitory interneurons. AP, area postrema; XII, hypoglossal nucleus; X, dorsal motor nucleus of vagus; C and EC, cuneate and external cuneate; NA, nucleus ambiguus; SNV, spinal nucleus of trigeminal; LRN, lateral reticular nucleus; IO, inferior olive nucleus; PMR, paramedial reticular nucleus. D: transverse section of thoracic spinal cord shows excitatory descending pathway (E) distribution from LRN and inhibitory descending pathways (I) from R, PMR, and ventromedial medulla. Preganglionic sympathetic neurons in intermediolateral horn (IML) are excitatory. Interneurons that may modulate IML activity have been described. Gebber and McCall (235) in 1976 described excitatory interneurons near preganglionic neurons that are not activated antidromically but by stimulating medullary pressor sites ~10 ms earlier than antidromically driven preganglionic neurons. McCall et al. (446) in 1977 described neurons in intermediomedial region (IMM) of spinal gray that inhibit preganglionic excitatory neurons (believed to be inhibitory interneurons). [A and D adapted from Körner (365); B adapted from Spyer (594); C adapted from Loewy et al. (407).]

in the medulla, e.g., A1 neurons in the ventrolateral part of the lateral reticular nuclei, the raphe nuclei, or the paramedial reticular nuclei (131); 3) activating intermediomedial nuclei in the spinal cord, which may function as inhibitory interneurons (446); 4) inhibiting preganglionic sympathetic neurons through bulbospinal pathways; and 5) inhibiting excitatory neurons in the lateral reticular formation.

Efferent connections from the NTS may also mediate excitatory sympathetic responses during stimulation of chemoreceptors, somatic receptors, or the diving reflex.



MEDULLARY EXCITATORY (PRESSOR) REGIONS. These regions activate predominantly preganglionic sympathetic neurons in the intermediolateral horn. The lateral and ventrolateral reticular nuclei, which have excitatory descending pathways in the dorsolateral part of the dorsal funiculus, are the major excitatory neurons in the medulla. The parvocellular nucleus also causes sympathetic cardiac acceleration (365).

Efferents from the NTS to lateral reticular nucleus may excite these reticular neurons in response to stimulation of chemoreceptors or somatic receptors or inhibit them in response to baroreceptor stimulation.

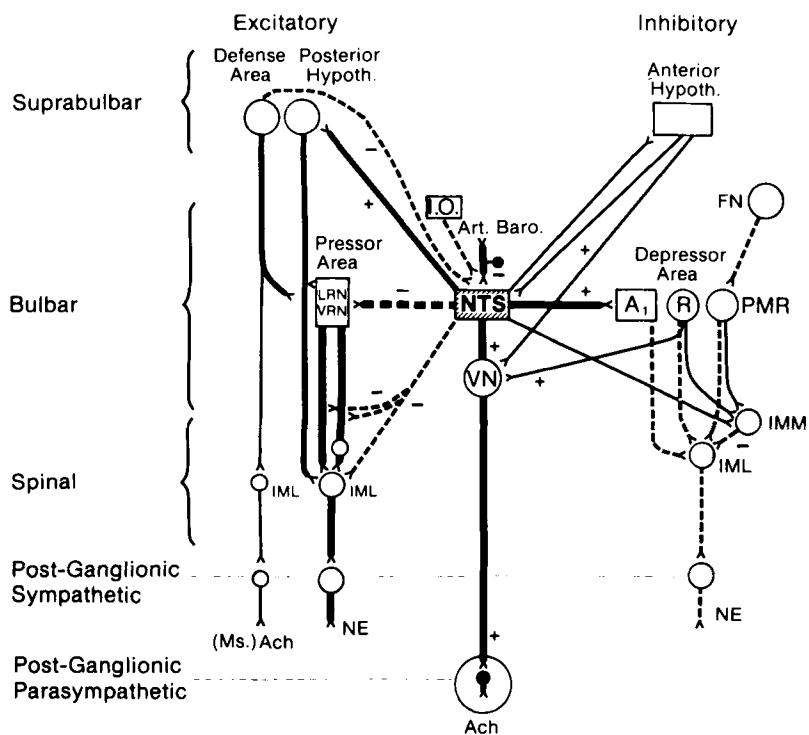


FIG. 9. Excitatory and inhibitory pathways regulating medullary pressor and depressor areas and preganglionic spinal sympathetic neurons (IML, IMM) and preganglionic medullary vagal neurons (VN). VRN, ventral reticular nuclei; A1, inhibitory noradrenergic neurons in ventral part of LRN; NE, norepinephrine; Ach, acetylcholine; Ms, skeletal muscle; Art. Baro., arterial baroreflex. Solid lines, pathways that stimulate neurons; dotted lines, pathways that suppress neurons.

Excitatory input from the posterior hypothalamus, the defense area, the fastigial nucleus, and other parts of the midbrain or forebrain may also regulate their discharge.

NUCLEUS TRACTUS SOLITARIUS. The neurons of the NTS in the medulla are probably the most important in the integration of sensory input from various afferent pathways and in the modulation of reflex cardiovascular and respiratory as well as other functions. Impulses originating in arterial or cardiopulmonary baroreceptors and in chemoreceptors travel in glossopharyngeal and vagal afferent fibers with cell bodies in the petrosal and nodose ganglia and terminations in the NTS (44, 291, 385, 469). The NTS receives input also from other cranial nerves (496) (e.g., trigeminal, facial, and vestibular) from the hypothalamus (555) (e.g., paraventricular and posterior hypothalamic nuclei) from the brain stem (602) (e.g., locus ceruleus) and from the intermediolateral nuclei in the spinal cord (555). Figures 8A and 9 show these pathways.

Humoral factors in blood and cerebrospinal fluid may influence the NTS because of its vascular and neural communications with the area postrema, which is near the ventricular system and does not have a blood-brain barrier (493).

Efferent fibers from the NTS project to three major groups of cardiovascular neurons (Figs. 8A, 9): 1) vagal preganglionic nuclei in the medulla (406, 498) and sympathetic preganglionic nuclei in the intermediolateral nucleus of the spinal cord (406); 2) other brain stem nuclei, such as the parabrachial nucleus and the

reticular formation (406, 497, 526); and 3) higher centers in the forebrain, particularly the hypothalamus and the amygdala (526).

Structural and biochemical features of the NTS. In his review Palkovits (493) indicated that cardiovascular neurons represent only a small portion of the NTS.

The NTS itself occupies only a small portion of the entire medulla (<5%) and is very cellular. It extends over almost the entire length of the medulla oblongata. The cells in the medial part just before and after the obex are involved in blood pressure regulation because a lesion in this area causes hypertension and microinjections of norepinephrine decrease arterial pressure (170, 171). This area has ~20,000 neurons (493). Although no exact data are available on the number of synaptic terminals, Chiba and Kato (104) estimated ~2,000 presynaptic terminals in a 6,800- μm^2 surface area. With this estimate Palkovits (493) deduced that there are ~20–30 million nerve terminals subserving cardiovascular regulatory functions in the NTS.

Biogenic amines have been demonstrated in the NTS by histochemical and immunocytochemical as well as biochemical methods. According to Dahlstrom and Fuxe (145) norepinephrine-containing neurons are present in areas caudal to the obex and in the area of the dorsal medulla close to the vagal nuclei in the rat. This group of ~1,000, referred to as the A2 cell group (600), and the locus ceruleus (602) are the major sources of catecholaminergic terminals found on NTS neurons or on primary cardiovascular afferent fibers in the NTS (104). Thus these terminals may regulate the input and output of the NTS.

Hökfelt et al. (300) identified the enzyme phenylethanolamine *N*-methyltransferase, which converts norepinephrine to epinephrine, with immunocytochemistry in neurons of the rostral part of the NTS. Although there are fewer adrenergic neurons than noradrenergic neurons in the NTS, this nucleus has higher concentrations of epinephrine and phenylethanolamine *N*-methyltransferase than any other part of the CNS (390, 547, 649). Prostaglandin concentrations (140) are also high in the NTS, but serotonin and choline acetyltransferase contents are low (353, 495). Nerve terminals in the NTS may contain vasopressin, probably originating in the hypothalamus (588), substance P (141), and enkephalin (647).

Functional role of NTS and other brain stem nuclei in cardiovascular control. Physiological responses to interventions in the NTS are significant and regulate arterial pressure, heart rate, and vascular resistance. Four examples follow. 1) Electrolytic lesions of the NTS cause a sustained elevation of arterial blood pressure (469, 523) associated with loss of arterial baroreflex responses but with normal renin and aldosterone levels (523). Clonidine, the α_2 -agonist (534), which inhibits sympathetic activity, and α_1 -adrenergic blockers reverse the hypertension. 2) Hypertension is also caused by destruction of adrenergic pathways to the NTS with CNS injections of 6-hydroxydopamine in rats or with lesions of the A2 neurons (523). 3) Talman et al. (608, 609) propose that glutamic acid may be the mediator of baroreflexes in the NTS. It is densely distributed in this area and may be released by electrical stimulation of the central end of the cut vagi. Small amounts injected into the NTS cause hypotension and bradycardia. Larger amounts of L-glutamic acid or its agonist, kainic acid, cause severe hypertension and inhibit baroreflexes, presumably by blocking L-glutamic acid receptors. 4) Gamma-aminobutyric acid (GABA) is an inhibitory transmitter in the spinal cord, in the nucleus ambiguus, and also in more rostral areas of the brain (173, 198). Administered into the cerebral ventricle in small amounts, the GABA agonist, muscimol, causes bradycardia, hypotension, and a decrease in renal sympathetic nerve activity (41). Bicuculline, the GABA-receptor antagonist, reverses these effects. Thus GABA receptors in the region of the forebrain may have an important inhibitory role on sympathetic drive.

On the other hand GABA and muscimol in the brain stem restrain vagal neurons in the nucleus ambiguus and cause cardioacceleration. Microinjection of bicuculline, the GABA blocker, into this nucleus disinhibits vagal neurons, causing bradycardia and hypotension; muscimol reverses the hypotension (173). This action is specific because muscimol does not reverse the bradycardia and hypotension caused by clonidine, which activates central α_2 -receptors.

Thus GABA and muscimol may cause opposite effects on heart rate and arterial pressure, depending on their site of action. They inhibit the sympathetic out-

flow in the forebrain, causing hypotension and bradycardia, and inhibit parasympathetic outflow in the brain stem, causing hypertension and tachycardia.

Projection of baroreceptor afferents to brain stem. Neurophysiological and anatomical studies indicate that the NTS receives myelinated and unmyelinated afferents from the arterial baroreceptors and from the cardiac receptors with vagal afferents (44, 183, 228, 291, 329, 330, 385, 444, 469). Evoked potentials at the same site in the NTS during stimulation of aortic and sinus nerve afferents confirm a common region for the first synapse (60, 229), but single-unit recordings do not indicate that convergence from these two afferents occurs on the same neurons in the NTS (594). However, other medullary neurons outside the NTS show convergence of evoked potentials (61). Thus the inhibitory interaction between these afferents may result from convergence at a stage in the reflex pathway beyond the NTS. When conditioning stimuli are delivered to one of the two afferents and the NTS is stimulated to evoke antidromic potentials in the other nerve, there does not appear to be an interaction. This supports the view that the interaction between aortic and carotid baroreflexes is postsynaptic either at the first synapse or at subsequent synapses in the reflex pathway (229, 330).

Hypothalamus and Cardiovascular Control

The hypothalamus plays a major role in cardiovascular regulation through its multiple connections with cardiovascular neurons in the brain stem and with preganglionic vagal and sympathetic neurons. Emotional stimuli and behavioral patterns originating in the hypothalamus may have significant circulatory effects and stimulating or damaging hypothalamic nuclei may modify cardiovascular reflexes and exert significant and sustained changes in blood pressure. Mancia and Zanchetti (428) have recently published an excellent extensive review on this subject.

ELECTRICAL STIMULATION OF HYPOTHALAMUS. Electrically stimulating different parts of the hypothalamus causes significant pressor or depressor responses (Figs. 9, 10). The pathway responsible for the pressor response begins in the supraoptic region, continues to the level of the optic chiasm in the lateral hypothalamus, then to the medial and ventral structures around the third ventricle, and gradually extends dorsally to the fields of Forel and the posterior hypothalamic nucleus (94, 106). The most marked pressor effects can be observed at the level of the lateral hypothalamus.

Depressor responses, evoked by stimulating a much more rostral part of the hypothalamus, begin in the preoptic area and extend into the septum and nearby structures, primarily including the anterior hypothalamic nuclei (218, 292).

Both sympathetic and vagal mechanisms are involved, the latter mostly in the depressor response.

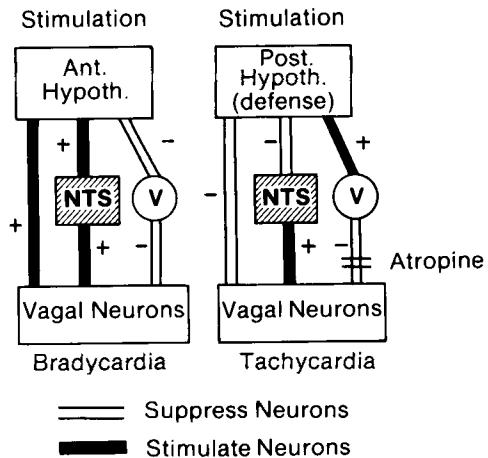


FIG. 10. Activation of vagal neurons by anterior hypothalamus (Ant. Hypoth.) and NTS causing bradycardia (*left*) and inhibition of vagal neurons by the posterior hypothalamus (Post. Hypoth.) and by respiratory neurons causing tachycardia (*right*). V, respiratory neuronal activity that inhibits vagal neurons causing tachycardia; atropine blocks this inhibition.

STIMULATION OF POSTEROLATERAL HYPOTHALAMUS PRESSOR AREA. Stimulating the pressor regions causes hypertension, tachycardia, constriction of resistance vessels in intestine, kidney, and skin, and constriction of splanchnic capacitance vessels (110, 194, 203), but vasodilatation in skeletal muscle (175, 648). The latter occurs through activation of a sympathetic vasodilator pathway (Fig. 9).

Sympathetic vasodilatation. Uvnäs, Folkow, and others have demonstrated that electrically stimulating the lateral and posterior hypothalamus activates this specialized section of the sympathetic nervous system characterized by a cholinergic vasodilatation in skeletal muscle (69, 175, 194, 219, 648). Uvnäs (648) and Bolme and Fuxé (69) demonstrated that cholinergic sympathetic fibers innervate skeletal muscle resistance vessels in several animal species. This innervation may be lacking, however, in nonhuman primates. Schramm et al. (567) reported that electrical stimulation of the pressor hypothalamic area of the monkey is accompanied by vasodilatation in skeletal muscle, but the mediator is not cholinergic. Increased circulating epinephrine and activated β -receptors may in part mediate the dilatation (380, 566).

In humans active vasodilatation may occur in skeletal muscle of the forearm during emotional stress (67). Active reflex vasodilatation also occurs in humans after adrenergic blockade (8, 10, 440) and in patients with autonomic neuropathy (52, 358) during the Valsalva maneuver, application of ice on the forehead (8, 10, 358), or simulated diving by apneic facial immersion (52). These reflexes ordinarily cause vasoconstriction when adrenergic sympathetic efferent pathways are intact and may reflect an integrated response of emotional hypothalamic stimuli and other excitatory reflexes. The vasodilatation in humans may be partly cholinergic (8, 10, 52, 67, 440) and partly

noncholinergic if sympathetic vasoconstrictor tone is withdrawn or noncholinergic sympathetic pathways are activated, as were those reported by Schramm et al. (566, 567) in the monkey.

Electrically stimulating efferent sympathetic nerves in animals after adrenergic blockade may induce vasodilatation that is cholinergic in skeletal muscle but noncholinergic in other vascular beds, e.g., the paw of the dog (3, 9, 46, 50), where noncholinergic dilatation occurs even without adrenergic blockade (9) and may be involved in certain reflex responses (46). Nonneuronal histamine may also indirectly mediate a vasodilator response in skeletal muscle during stimulation of baroreceptors (50, 79).

Defense reaction. Abrahams et al. (22, 23) suggested that the characteristic cardiovascular pattern elicited by stimulating the pressor area in the hypothalamus (including hypertension, tachycardia, and vasoconstriction in all vascular beds except iliac bed, where dilatation occurs) may have behavioral significance. They showed that stimulating the hypothalamic areas that elicit this pattern of responses also causes (in absence of anesthesia) a definite behavioral reaction consisting of pupillary dilatation, piloerection, snarling, unsheathing of the claws, and sudden attack. Thus the characteristic cardiovascular responses triggered from a specific area of the hypothalamus have been considered the cardiovascular component of defense or emotional behavior.

Descending hypothalamic pathways. Gebber et al. (237) suggest that the descending excitatory pathways from the hypothalamus follow two tracts. One connects with the medullary neurons and activates sympathetic fibers, and the other seems to bypass the medullary excitatory area and reach preganglionic sympathetic neurons directly.

Another important descending hypothalamic pathway is that mediating cholinergic vasodilatation. Lindgren et al. (395) reported that stimulating various sites below the hypothalamus could reproduce the cardiovascular defense response. These sites include the midbrain tegmen, the substantia reticularis of the pons, and a narrow strip in the medulla close to the dorsal surface (130).

Abrahams et al. (22) indicated from studies in unanesthetized cats that the midbrain tegmen may trigger both the cardiovascular and the behavioral components of the defense reaction, just as when the hypothalamus is stimulated. They described another midbrain area located dorsal to the cerebral peduncle as the pathway for the cardiovascular but not the behavioral reaction. Destroying this area and not that of the tegmen abolished the vasodilatation elicited by hypothalamic stimulation.

Stimulating the motor cortex may cause isolated cholinergic muscle dilatation in cats (195). The responsible pathway courses through the internal capsule and relays in the cholinergic vasodilator area of the hypothalamus. Ellison and Zanchetti (196) suggest

that conditioned movements of the limbs, exercise, and hypothalamic-mediated cholinergic dilatation may be linked under certain experimental conditions.

These cholinergic pathways may course directly from the hypothalamus to preganglionic sympathetic neurons in the spinal cord or, as suggested by Takeuchi and Manning (607), participate in the baroreceptor reflexes in the medullary vasomotor area. Histaminergic vasodilator pathways from the hypothalamic defense area have also been described (380). The course of these fibers is presumably close to the cholinergic fibers.

Postganglionic cholinergic neurons. Withdrawing sympathetic constrictor tone and activating cholinergic sympathetic neurons increases skeletal muscle flow during the defense response (130, 301). Horeyseck et al. (301) showed that stimulating areas of the hypothalamus that cause cholinergic vasodilatation in skeletal muscle also evokes a discharge in normally silent postganglionic muscle units that are not activated by sympathetic reflexes. These dilator neurons are not activated during stimulation of hypothalamic sites that cause vasoconstriction, in contrast to constrictor neurons, which are activated. During cholinergic vasodilatation the constrictor neurons may be silent briefly or have a transient burst of activity followed by prolonged suppression. The pattern of activity of these constrictor neurons may vary, depending on the vascular bed they innervate. In the cutaneous bed there is continuous excitation of these neurons when both hypothalamic constrictor or cholinergic dilator pathways are stimulated.

Feeding center. Electrical stimulation in a hypothalamic area dorsal to the defense area in the lateral hypothalamus causes the unanesthetized cat to behave as if in search of food and to eat (220). After anesthesia the same stimulus increases intestinal motility and intestinal blood flow, reduces gastric motility and muscle blood flow, and moderately raises arterial pressure and heart rate.

Thus discreet areas in the hypothalamus can modulate the distribution of blood flow to effectuate specific behavioral functions, conferring on the hypothalamus a significant modulatory role in the control of autonomic cardiovascular responses.

STIMULATION OF ANTERIOR HYPOTHALAMUS DEPRESSOR AREA. Stimulating rostral parts of the hypothalamus produced responses that Hilton and Spyer (292) described as depressor with vagally mediated bradycardia and vasodilatation similar to those seen with stimulation of baroreceptors. In contrast to the posterior hypothalamus the anterior hypothalamic area has no direct connection with sympathetic preganglionic neurons and no visible behavioral responses. It has direct connections with vagal medullary neurons and with the NTS, however (Fig. 10). Inhibition of respiration during anterior hypothalamic stimulation may contribute to the bradycardia (292). Behavioral components of rostral stimulation may be the playing-

dead reaction in frightened animals (408) and emotional fainting in humans (47, 428). The powerful cardiovascular restraining influence of this region is unquestionable, however, in view of the fulminant hypertension that is provoked in rats after the anterior hypothalamus is destroyed (476).

LOCOMOTOR BEHAVIOR AND CENTRAL COMMAND. Electrically stimulating areas in the subthalamic region (H_2 field of Forel and preventricular gray) in conscious dogs or cats causes significant increases in heart rate, cardiac output, and arterial pressure as well as hyperventilation (193, 545). The cardiovascular and respiratory changes are associated with locomotion and running movements such as with exercise. It is important, however, that these cardiorespiratory changes may be seen in the absence of any locomotion or muscle contraction in animals that have been anesthetized or paralyzed. Thus the autonomic drive did not depend on any feedback mechanism either from the exercising muscle or from chemo-, arterial, or cardiopulmonary receptors. Eldridge et al. (193) reported that the locomotor (electromyogram or femoral nerve activity) and respiratory (phrenic nerve activity) drives increased in parallel based on the intensity of stimulation (Fig. 11).

Krogh and Lindhard (373) postulated in 1913 that the cardiovascular and respiratory responses during the initial stages of exercise are triggered by impulses originating in the higher motor centers, which "irradiate" to the medullary controllers.

Several experimental observations in humans (225, 247, 464, 542) support this concept and emphasize the relative contribution of the central-command and peripheral mechanisms to the cardiovascular response to static exercise.

CENTRAL COMMAND VERSUS SOMATIC AFFERENTS DURING EXERCISE. Rusch et al. (544) recently reported that isometric handgrip exercise at 30% of maximal voluntary contraction in humans causes an abrupt increase in heart rate and arterial pressure with vasoconstriction predominantly in the calf vessels. If just before static contraction is terminated a cuff is inflated around the arm to arrest the circulation in the exercising forearm, the arterial blood pressure remains elevated, heart rate drops back to control, and the opposite forearm and calf vessels are significantly constricted for as long as the cuff is inflated. Thus the arterial pressure can be maintained probably by activation of sensory endings in the exercising muscle, the result of an accumulation of metabolites trapped by the cuff occlusion. In addition to the reflex from the active ischemic muscle, there must be a central command from higher, possibly cortical centers to the cardiovascular and respiratory center in the brain stem. The sudden reduction in heart rate, the transient fall in pressure, and the sudden marked increase in forearm vascular resistance as soon as exercise is terminated may indicate the cessation of central com-

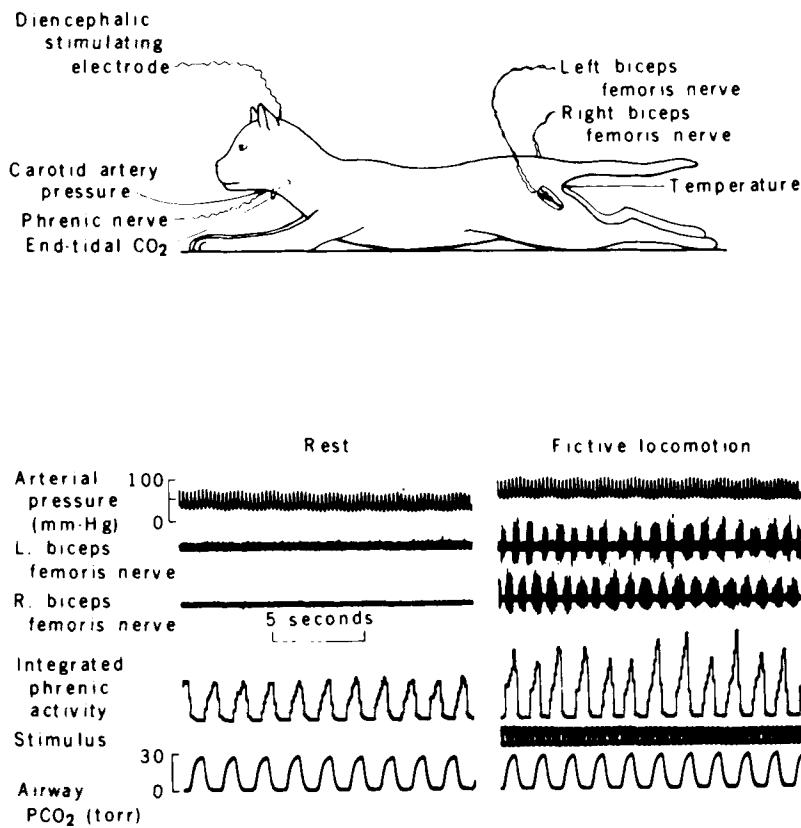


FIG. 11. Electrical stimulation of diencephalon in decorticate paralyzed cats triggers simultaneously central hyperventilation (increased phrenic nerve activity) and increased motor activity of both biceps femoris nerves. Hyperventilation clearly does not depend on peripheral stimulus from contracting muscle or chemoreceptors. [From Eldridge et al. (193).]

mand. Apparently the tachycardia and the increase in blood flow to the contralateral forearm of humans during contralateral isometric handgrip, which are reversed abruptly when contraction ceases despite the persistence of the peripheral somatic afferent stimulus, might be attributed to activation of the locomotor subthalamus area, as described in animals (193, 545).

Mitchell et al. (464), contrasting the response to exercise in small and large groups of muscle and in strong and weak muscle, concluded that increasing static exercise of a small or weak group of muscle from 20% to 40% maximum voluntary contraction can significantly increase pressure and heart rate similarly, as with larger or stronger muscle. However, the absolute levels are higher with stronger and larger muscles. The results indicate that the contribution of central command depends more on the amount of central activity necessary to recruit motor units. Other work related to somatic afferents and central command is discussed in *Reflexes Originating in Skeletal Muscle During Exercise*, p. 705.

INTERACTIONS OF HYPOTHALAMUS WITH BARORECEPTORS AND CHEMORECEPTORS. In 1957 Gellhorn (238) reported the influence of lesions of the hypothalamus on the baroreflex, proposing that the anterior hypothalamus facilitated the reflex. Since then several electrophysiological and functional studies have documented the interactions between the hypothalamus and arterial baro- and chemoreceptors. Earlier hypo-

thalamic stimuli as well as baroreceptors and chemoreceptors were shown to affect cardiovascular function. However, does stimulation of the arterial baroreceptors or chemoreceptors activate neurons in the hypothalamus?

According to Thomas and Calaresu (628) and Spyer (593), stimulating the carotid sinus nerve increases the firing rate of neurons in the posteromedial as well as rostral depressor area. Thomas and Calaresu (628) also reported an increased electrical activity in the posteromedial hypothalamus during carotid chemoreceptor stimulation with cyanide. These findings extend the earlier results obtained by Bartorelli et al. (49) that show an inhibition of hypothalamic autonomic activity and sham-rage behavior by carotid baroreceptor stimulation and by Bizzi et al. (65) that show increased activity during chemoreceptor stimulation.

These effects are probably all due to ascending polysynaptic pathways from the NTS to the ascending reticular system in the hypothalamus (493). More recently Calaresu and Ciriello (94, 106) showed that hypothalamic units in the paraventricular and supraoptic nuclei are activated more intensely during carotid sinus nerve stimulation than aortic depressor nerve stimulation (94). In turn stimulating paraventricular and supraoptic nuclei causes tachycardia and hypertension and inhibits the reflex bradycardia elicited by carotid sinus but not aortic nerve stimulation (106). These experiments indicate that neurons of the

NTS may modulate vagal and sympathetic efferent activity through long bulbar and suprabulbar tracts that communicate with hypothalamic and forebrain structures.

FACILITATING OR SUPPRESSING REFLEX RESPONSES BY HYPOTHALAMIC STIMULATION. Whether hypothalamic stimulation facilitates or suppresses reflex responses depends on the site of stimulation.

Facilitation of reflex bradycardia. Stimulating the anterior hypothalamus causes bradycardia, hypotension, and decreases in ventilatory drive (292). These responses are similar to those caused by stimulating the baroreflex, hence the facilitatory interaction between the two stimuli.

For over 25 years the anterior hypothalamus has been known to facilitate the baroreceptor reflex; direct evidence for such an interaction has since come from electrically stimulating the anterior hypothalamus preoptic region and the septum in the cat (234). Part of this area corresponds to the anterior hypothalamic depressor area identified from the similarity of the response to the baroreceptor reflex (292). Anterior hypothalamic stimulation evokes a vagal bradycardia that summates with the response to aortic nerve stimulation (200). Both stimuli excite vagal preganglionic neurons in the dorsal motor nuclei of the vagus and interneurons. Similar responses are seen during stimulation of the amygdala, septum, midbrain, and hippocampus (234, 295). Kaufman et al. (341) suggest a role for the lateral subthalamus in the vagal bradycardia evoked by aortic nerve stimulation. A facilitatory loop in baroreceptor vagal control probably connects the NTS to this subthalamic region (524).

Also this facilitation may be related in part to the inhibition of respiration evoked by stimulating this hypothalamic depressor area (292). Inhibiting inspiration and apnea increase vagal activity.

Korner et al. (364, 368) reported that the bradycardia induced by severe hypoxia is prevented in pontine rabbits (where hypothalamic medullary pathways are cut) but not in thalamic rabbits (where lesion is rostral to hypothalamus). Thus suprapontine structures are critical to the chemoreceptor reflex bradycardia. Apparently, eliminating the input from the anterior hypothalamus can significantly attenuate the baroreflex and the bradycardia of the chemoreflex, arguing for its involvement in the integrated responses to baroreceptor and chemoreceptor reflexes.

Facilitation of reflex pressor and vasoconstrictor responses. In contrast to the inhibitory influence of the anterior hypothalamic region, the posteromedial hypothalamus and the defense area are excitatory and should facilitate excitatory stimuli. The work of Manning (431), Kent et al. (344), and Reis and Cuénod (524) indicates that posterior hypothalamic stimulation may facilitate the excitatory pressor response to carotid occlusion, reflecting the suprapontine contribution to this excitatory response.

Kumada et al. (375) provide another example of enhancement of excitatory responses by showing that the reflex vasoconstrictor responses of the renal and mesenteric beds to carotid sinus hypotension are enhanced more than twice during electrical stimulation of the defense area of the hypothalamus. This interaction is specific, because the vasoconstrictor response to carotid hypotension in the hindlimb is not augmented but appears attenuated.

Suppression of reflex bradycardia by the hypothalamic defense reaction. Stimulating the excitatory defense area of the hypothalamus inhibits the reflex bradycardia mediated through arterial baroreceptors and cardiopulmonary receptors (236, 304, 672). Thomas and Calaresu (629) reported a similar inhibition of the bradycardia caused by chemoreceptors. Apparently, reflex effects on gastric motility and tone through vagal efferents are also inhibited (672, 673). Because most pressor responses evoked by central stimulation are associated with tachycardia and hyperpnea along with the rise in pressure, they would be expected to inhibit the baroreflex control of heart rate. This is observed with stimulation of the midbrain (374) or the amygdala (640). Clearly there is an antagonistic interaction with respect to the efferent vagally mediated reflexes. On the other hand there is some controversy with respect to the baroreflex withdrawal of sympathetic efferent activity. Gebber and Snyder (236) reported that the defense reaction does not oppose the baroreflex-mediated inhibition of sympathetic tone and vasodilatation. The work of Kumada et al. (375) and others (174) indicates that the inhibitory influence of the baroreceptors on sympathetic activity is not influenced by the excitatory influence from the posterior hypothalamus. This is contrary to the report by McAllen (442) and others (594) that baroreflex inhibition of sympathetic activity is ineffective during stimulation of the defense area.

What is the site of interaction between the defense area and the vagally mediated efferent activity? It appears that the sensory receptors are not involved but that the projections to the NTS may be under presynaptic control (669) and stimulating the defense area may inhibit the activation of NTS neurons (26, 442).

Other sites of interaction along the neuraxis from the medulla to the hypothalamus are probably also involved. The possibility that the respiratory "gate" may prevent stimulation of vagal neurons is plausible because pronounced hyperpnea and inspiratory drive accompany the defense reaction. The posterior hypothalamus may also have a direct inhibitory influence on vagal neurons (414). Thus three processes appear to inhibit the vagal neurons during the defense reaction, causing tachycardia: 1) direct inhibition from the posterior hypothalamus, 2) hyperpnea and increased inspiratory drive, and 3) suppression of NTS activity, which ordinarily excites the vagal neurons.

Jordan et al. (328) showed that iontophoresis of

atropine blocked the inspiratory vagal inhibition but not the effect on the NTS nor the direct hypothalamic effect on vagal neurons (Fig. 10).

Inferior Olive: Suppression of Baroreflex

In 1966 Smith and Nathan (585) reported that stimulating a region of the inferior olive in the medulla completely inhibits the baroreceptor reflex during carotid sinus stretch; they suggested that this area of the olive mediates the baroreceptor reflex inhibition by the defense area.

Histological studies (555) support the presence of a descending pathway between the hypothalamus and the particular site of the olivary complex involved in inhibiting the baroreflex.

This inhibition also might be mediated through the anterior lobe of the cerebellum (403, 471), which inhibits autonomic reflexes in general and baroreflexes in particular.

In his review Spyer (594) refers to unpublished work of J. H. Coote that confirms that inferior olive stimulation inhibits the baroreflex during carotid hypertension but does not support its role or that of the cerebellum in the hypothalamic defense reaction or in the interaction between the defense reaction and the baroreflexes. This is because neither lesions of the inferior olive nor cerebellectomy prevent the defense area-baroreflex interaction.

Furthermore stimulating the inferior olive, which prevents the baroreflex response to carotid hypertension, apparently does not modify the response to carotid occlusion significantly, yet lesions in that area cause significant progressive increments in arterial blood pressure and sustained hypertension. This region's influence on neurogenic hypothalamic control is not fully understood despite its significant influence on the baroreflex and on arterial pressure.

Cerebellar Control: Hypothalamic and Baroreceptor Interactions

Stimulating the fastigial nucleus of the cerebellum causes hypertension and tachycardia (400, 468). The pattern of circulatory response to fastigial stimulation is similar to that of unloading the baroreceptors during hypotension or hemorrhage, which causes reflex vasoconstriction and tachycardia (400). Circulatory adjustments to upright posture might result not only from arterial and cardiopulmonary baroreceptor reflexes but also from reflex responses to afferent impulses originating in the vestibular apparatus, which pass to the fastigial nucleus.

Sectioning the fastigiobulbar tract or the paramedian reticular nucleus in the medulla eliminates the pressor response to stimulation of the fastigial nucleus. Because the paramedian reticular nucleus inhibits sympathetic activity and may mediate the sympathetic inhibition of the baroreflex, Lisander and Martner (401) suggested an inhibitory interaction between

the fastigial and baroreceptor fibers on the cells of the paramedian reticular nucleus. Nathan (475) showed an inhibitory interaction between these two stimuli with respect to the final efferent output as it was recorded over the splanchnic nerve.

Zanchetti and Zoccolini (683) reported that stimulating the fastigial nucleus of the thalamic cat evoked a burst of sham rage in addition to a rise in pressure and tachycardia. These effects may be relayed through the hypothalamus, and, like the posterior hypothalamic stimulation and the defense reaction, the stimulus inhibits the cardiac vagal component of the baroreceptor reflex (24, 294). Thus stimulating the fastigial nucleus causes 1) sham rage, 2) hypertension and tachycardia, and 3) increased sympathetic drive possibly by suppressing the paramedian reticular nuclei or the influence of baroreceptors on the paramedian reticular nuclei and prevents 1) cholinergic vasodilatation and 2) baroreflex bradycardia. In contrast, stimulating the white matter of the cerebellar anterior lobe results in inhibitory responses: 1) it prevents the pressor response and cholinergic dilatation of defense reaction; 2) it prevents the baroreceptor and chemoreceptor reflexes; and 3) it prevents cardiovascular and respiratory responses. Despite these major autonomic influences uncovered during cerebellar stimulation, cerebellectomy does not suppress the defense reaction or baroreflexes.

Suprabulbar and Cortical Connections

Korner (365) has briefly reviewed these pathways. Ascending projections from the medullary reticular formation course through the midbrain, traverse the hypothalamus, and send fibers to the septum, the amygdala, and the basal ganglia (see Fig. 8). Other ascending pathways reach the orbital frontal cortex or the gyrus cinguli via the dorsal and anterior thalamic nuclei, respectively. Electrically stimulating these sites can induce significant autonomic responses, and the afferent input into these regions is integrated to modulate the influence of behavioral and emotional stimuli on cardiovascular responses and allow an optimal circulatory adjustment.

Information on the autonomic effects of stimulating the hypothalamus, inferior olive, cerebellum, and their descending pathways is more plentiful than that on the cortical descending pathways and their autonomic influences (297, 298). In 1951 Wall and Davis (659) described three cortical systems affecting autonomic function: one from the sensorimotor cortex along the pyramidal tract, a second from the orbital cortex through the hypothalamus, and a third from the anterior part of the temporal lobe to the pons. Stimulating these cortical areas and other subcortical areas such as the amygdala and septum induces either pressor or depressor responses (332), bradycardia, and apnea (641) and may be associated with particular behavioral patterns or with somatic inhibition (408,

641). A specific autonomic cortico-hypothalamic-spinal tract originating in area 4 in monkeys may mediate vasodilatation in skeletal muscle in association with the locomotor response (108). The noncholinergic vasodilatation in the monkey may have a cholinergic counterpart in canines (648).

The stimulus to the motor cortex may suppress the baroreceptor reflex-mediated bradycardia (25) and cause hypertension and tachycardia. Possibly the powerful respiratory drive evoked by the muscular response or in association with it may inhibit the vagal bradycardia and cause the hypertension.

Stimulating baroreceptors may decrease skeletal muscle tone in anesthetized animals (568, 642), decrease cortical electrical activity in awake dogs (71), and inhibit attacks of sham rage in cats (49). Coleridge et al. (124) have also reported that stimulating the carotid sinus baroreceptors in anesthetized cats causes prolonged inactivation of single cortical pyramidal tract cells. They suggested that a reflex operates through the reticular formation and inhibits cortical motor neurons.

Sleep and Sinoaortic Reflexes

Baccelli et al. (43) reported that desynchronized sleep [rapid eye movement (REM), or dreaming stage] lowered arterial pressure, reduced iliac conductance, and increased mesenteric conductance (Fig. 12). In animals with chronic sinoaortic denervation, sleep caused a much greater fall in arterial pressure and significant increases in mesenteric and iliac conductance. Thus the integrity of the baroreceptor reflex is necessary for the circulatory adjustment to REM sleep. In another group of animals these investigators

studied the response to carotid occlusion during REM sleep and found a reduced pressor response to carotid occlusion. Thus a marked and generalized vasodilatation, particularly in muscle blood vessels, that occurs during sleep is avoided and buffered by the intact though blunted baroreceptor reflex.

Respiratory Influences on Baroreceptor Control of Vagal Neurons

Anrep et al. (38, 39) showed that two mechanisms caused the respiratory-related fluctuations of heart rate: one had a central origin and was related to the genesis of respiratory activity; the other resulted from inhibitory sensory afferents activated during inflation of the lung. The excitability of cardiac vagal motor neurons may be influenced significantly by the respiratory activity. An inhibitory influence from the respiratory center may gate or block the excitatory input from other receptors. This could explain the marked suppression of the baroreceptor-mediated bradycardia by inspiration. Carotid sinus nerve stimulation prolongs the heart-rate period only if it occurs within expiration; it is ineffective or considerably less effective if it occurs during inspiration. Measurements of vagal efferent neuronal activity have confirmed this. In 1976 Davidson et al. (161) found that a single cardiac vagal efferent fiber fires with a rise in arterial pressure only during expiration, not during inspiration (Fig. 13). Similarly the baroreflex control of heart rate in humans is enhanced during expiration (188, 643). A chemoreceptor stimulus also evokes a bradycardia and activates vagal efferent fibers only if timed to occur during expiration (161).

The work of Jordan and Spyer (331) and Stroh-

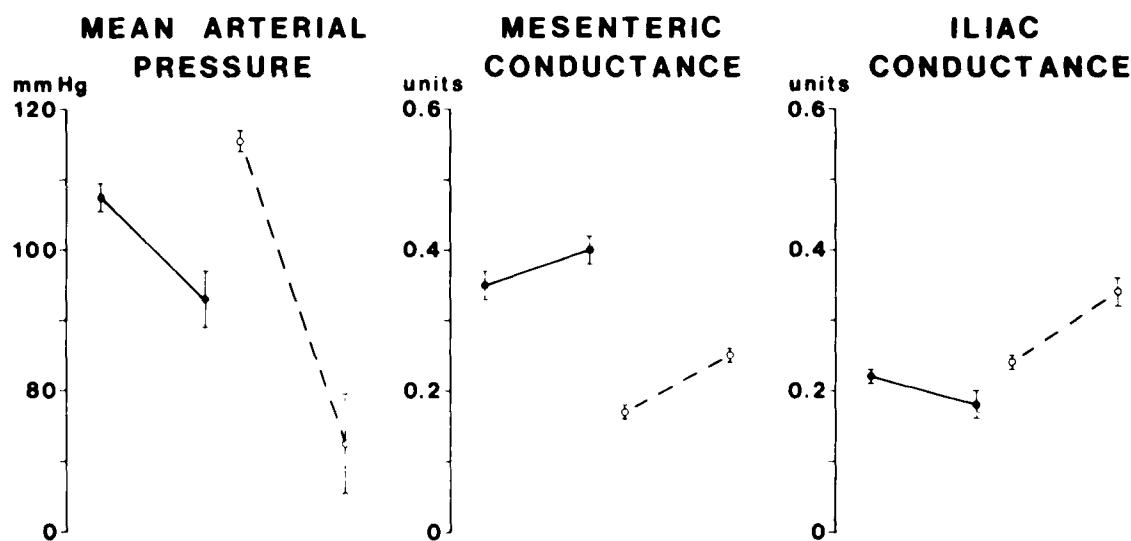


FIG. 12. Cardiovascular responses to desynchronized sleep (means \pm SE) before (solid lines) and after (dashed lines) sinoaortic denervation (6 episodes; 1 cat). Sleep induces hypotension, mesenteric vasodilatation, and iliac vasodilatation, but latter is reflexly buffered and reversed to vasoconstriction when baroreflexes are intact (solid lines). Sinoaortic denervation unmasks dilatation. [From Baccelli et al. (43), by permission of the American Heart Association.]

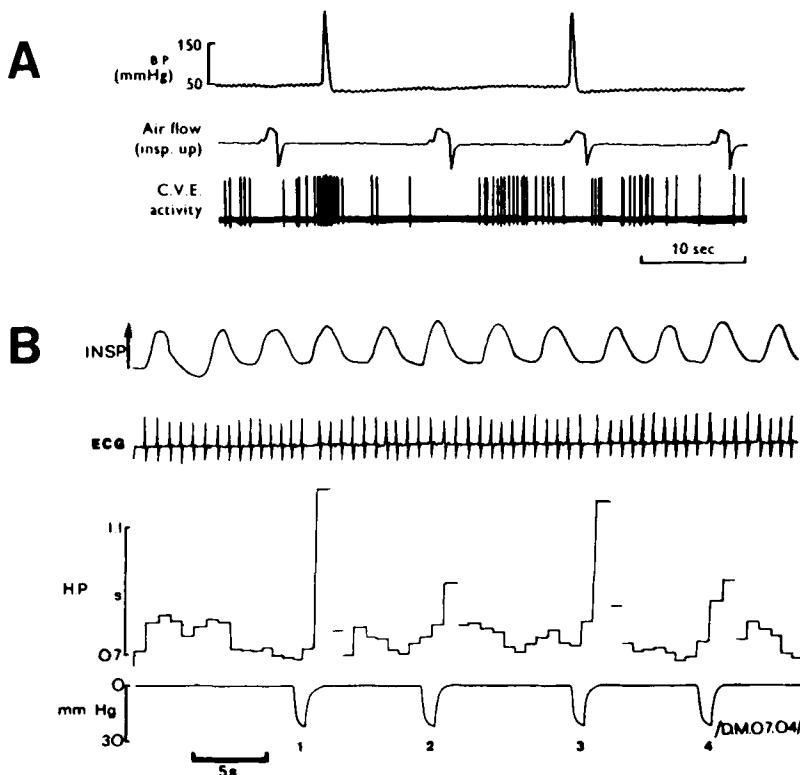


FIG. 13. A: carotid sinus blood pressure (BP), air flow, and single cardiac vagal efferent nerve (CVE) activity in dogs. Burst of firing caused by baroreceptor stimulation occurs only in expiration. B: effect of repeated brief baroreceptor stimulations by neck suction in humans (*lower tracing*) on RR interval (HP), during expiration (suctions 1, 3), and during inspiration (suctions 2, 4). Reflex bradycardia is greater during expiration. [A from Spyer (594); B adapted from Trzebski et al. (643).]

Werz et al. (598) suggests that gating, or the interaction between the respiratory afferents and the carotid and aortic afferents, occurs at a postsynaptic site. Although many preganglionic neurons show both respiratory and cardiac rhythm (235), many medullary neurons receiving chemoreceptor and baroreceptor input have no obvious respiratory rhythm (397). As McAllen and Spyer (444, 445) have shown, if iontophoresis of DL-homocysteic acid increases the excitability of vagal neurons, they will respond to either baroreceptors or chemoreceptors regardless of the respiratory cycle. Furthermore the antidromic potentials evoked in the carotid and aortic nerves by stimulation in the NTS do not vary in amplitude or threshold in phase with central respiratory drive or with lung inflation. These findings all suggest that the interaction, postsynaptic rather than presynaptic, occurs after the first synapse of sinoaortic nerves. McAllen, Jordan, and Spyer (443–445) suggest that the influence of respiratory activity occurs through pathways that directly impinge on the cardiovagal motor neurons. They also suggest that inspiratory neurons in the NTS may have a central inspiratory rhythm, be excited by lung inflation, and project to the nucleus ambiguus where the cardiovagal motor neurons reside.

Garcia et al. (231) demonstrated that atropine applied by iontophoresis blocks the inhibitory action of acetylcholine on cardiovagal motor neurons as well as the inspiratory-related depression of activity of cardiovagal motor neurons to DL-homocysteic acid. Small doses of atropine could cause a central bradycardia by

increasing vagal efferent activity if the animal had intact central or respiratory activity (339).

Respiratory activity may also influence the cardiac sympathetic preganglionic neurons (396). In vagotomized dogs the baroreceptor reflex regulation of heart rate is through sympathetic efferents and is reduced during inspiration. The suppression of sympathetic activity evoked by baroreceptor stimulation is minimal during phrenic nerve discharge and maximal shortly after inspiration ends (162). The baroreceptor sympathetic reflex has no respiratory gate, however, merely a change in the sensitivity to the inhibitory action of the baroreceptor reflex and a quantitative reduction in the effectiveness.

Spinal Preganglionic Sympathetic Neurons

These neurons are located in the intermediolateral horn of the thoracic and lumbar segments of the spinal cord. Their axons are mostly myelinated, leaving the spinal cord through the ventral root, separating to form the white rami, and synapsing in the paravertebral sympathetic ganglia in the sympathetic chain or in separate ganglia such as the celiac ganglion. Post-ganglionic fibers travel as individual nerves (e.g., cardiac and splanchnic) or rejoin the motor roots and are distributed to blood vessels in the peripheral nerve trunks. The discharge pattern of these neurons (firing frequency < 10 impulses/s) shows a clear cardiac rhythm. Distending one carotid sinus inhibits these neurons after a latency period of 148 ± 14 ms (132, 133).

Two types of spinal interneurons may influence the discharge of these preganglionic neurons. Brain stem stimulation at pressor sites excites both the interneuron and the preganglionic neuron at latencies of ~30 and 40 ms, respectively, suggesting that the excitatory interneurons mediate impulses to the preganglionic neurons (235).

More recently McCall et al. (446) described neurons in the intermediomedial region of the spinal gray, which are inhibitory interneurons, suppressing the preganglionic activity in the intermediolateral column. These interneurons are spontaneously active, have a cardiac rhythm, and are silenced by bilateral carotid occlusion. They apparently receive an excitatory input from the NTS, suggesting an inhibitory interneuronal function.

BRAIN STEM-SPINAL CORD CONNECTIONS. Specific pathways connect the brain stem reticular formation or specific nuclei with preganglionic sympathetic neurons in the intermediolateral horn. The pathways mediate excitatory and inhibitory influences.

EXCITATORY CONTROL. Stimulating the medullary pressor area (lateral and ventral reticular nuclei) excites the preganglionic sympathetic neurons in two different patterns, one with a short latency and the other with a long latency. Baroreceptor activation caused by a rise in arterial pressure or by stimulation in the depressor area of the medulla blocks the late response with long latency; conversely baroreceptors do not block the short-latency pathways (237, 587). These specific interactions may provide the electrophysiological explanation for some of our findings concerning the selectivity of the effect of carotid baroreflex activation in humans on certain vascular beds (7).

Hypothalamic and bulbar excitatory pathways activate preganglionic sympathetic neurons. Section of the dorsolateral funiculus that contains these pathways reduces blood pressure and abolishes cardiovascular responses to bilateral carotid occlusion in acute experiments. Chemoreceptor stimulation and inspiratory drive may excite preganglionic neurons through these descending excitatory pathways, which may also carry inhibitory fibers.

INHIBITORY CONTROL. As mentioned earlier the medullary depressor area encompasses three regions: the classic depressor region in the ventromedial reticular formation, a region near the ventrolateral border of the medulla (A1 region), and the caudal raphe nuclei containing serotonergic fibers (131). In 1975 Lipski and Trzebski (398) showed that some baroreceptor-sensitive neurons in the vicinity of the NTS can be activated antidromically by stimulation within the cervical spinal cord. The intermediomedial neurons of the spinal cord may be spinal inhibitory neurons in the baroreceptor reflex pathway (446).

Thus, stimulating the NTS could inhibit pregan-

glionic sympathetic neurons, either by inhibiting the neurons in the lateral reticular nucleus of the medulla, which are excitatory, by directly inhibiting sympathetic preganglionic neurons, or by directly stimulating inhibitory interneurons in the spinal cord (intermediomedial neurons).

Another inhibitory nucleus is the paramedian reticular nucleus in the ventromedial medulla. Descending pathways from this inhibitory region pass in the ventral funiculus of the spinal cord and tonically inhibit the preganglionic sympathetic neurons.

Stimulating the ventral area of the lateral reticular neurons reduces arterial blood pressure and inhibits preganglionic sympathetic neurons by activating the A1 group of norepinephrine-containing neurons. The inhibitory fibers from these neurons travel in the dorsolateral funiculus along with the descending excitatory pathways.

Thus the modulating influences of inhibitory and excitatory inputs from the medulla determine the discharge of the preganglionic sympathetic neuron in the intermediolateral column of the spinal cord. In turn the medullary neurons are modulated by input from the various sensory regions, but particularly from the NTS with its input from the arterial baroreceptors. The preganglionic neurons may also be influenced by interneurons either in the intermediomedial column of the spinal cord or possibly in the intermediolateral column and also by direct fibers from the hypothalamic region.

The final output of the preganglionic sympathetic fibers may integrate at several levels: spinal cord, bulbar region, hypothalamus, and probably even more rostral areas.

Medullary Preganglionic Vagal Neurons to Heart

The parasympathetic efferents originate in medullary neurons either in the dorsal motor nucleus of the vagus or the nucleus ambiguus. The relative distribution of the cardiac neurons in these nuclei varies in different species.

The influence of arterial baroreceptors on vagal preganglionic neurons is well documented (161), but there is considerably less information on the central mechanisms linking the baroreceptor afferent input to these neurons. Baroreceptor afferents terminate in the NTS, and the NTS projects to the nucleus ambiguus. However, the connections within the NTS and the nucleus ambiguus and the role of supramedullary connections in the normal reflex pathway remain unclear (443). There is both anatomical and physiological support for hypothalamic descending pathways to areas of the medulla that contain preganglionic vagal neurons, and the baroreflex control of preganglionic vagal neurons depends on the phase of respiration. Also, stimulating the anterior hypothalamus facilitates the vagal arm of the baroreceptor reflex, whereas stimu-

lation at many sites (particularly in medial and posterior regions of hypothalamus, fastigial nucleus, inferior olive, and other central sites) can suppress the vagal arm of the reflex.

Gebber and Klevans (234) in 1972 described facilitation of the baroreceptor vagal reflex in the cat by stimulation of the amygdala, septum, midbrain, and hippocampus.

Neuropeptides: Regulation of Arterial Pressure

Ganten et al. (230) and Palkovits (494) have reviewed this topic. Angiotensin, Leu-enkephalin, and substance P are some of the neuropeptides in the medulla, pons, hypothalamus, median eminence, etc. that contribute to the regulation of arterial pressure (494, 506). When injected into the cerebral ventricle, they cause hypertension and tachycardia and inhibit baroreflexes. Their hypertensive effect is caused primarily by increased sympathetic activity. Vasopressin, adrenocorticotropin, and corticosterone may contribute to the pressor effect of central angiotensin and Leu-enkephalin (64, 253, 539).

Various components of the renin-angiotensin system have been localized in brain nuclei (506), and increased renin activity was found in noradrenergic nuclei of spontaneously hypertensive rats (SHR), including A1 and A5 neurons, and in the NTS (230). Supersensitivity to central angiotensin in SHR may be related to increased receptor density or affinity in the area of the hypothalamus (506). Central injection of saralasin, the angiotensin-receptor blocker, or a converting-enzyme inhibitor lowers blood pressure in SHR (306, 429). The greater effectiveness of these drugs when given centrally rather than peripherally supports the dominance of the neurogenic mechanism in the action of these hormones.

The vasoactive intestinal polypeptide is another potentially important neuropeptide because its highest concentration is in the NTS (532, 579). When given intracerebrally it causes acute hypertension (494). The role of these and several other peptides found in various concentrations in different parts of the CNS (e.g., somatostatin, oxytocin, β -endorphin, α -melanotropin, bradykinin) is not clear. According to Palkovits (494) some neuropeptides may alter the rate of discharge and the sensitivity of noradrenergic neurons in the brain stem and others may have postsynaptic effects through the activation of the cyclic adenosine monophosphate (cAMP) system.

Brain Amines: Reflex Control

CATECHOLAMINES. Chalmers (101) has an excellent brief review on this subject. Central catecholaminergic nerves are important in the regulation of arterial blood pressure and in the reflex control of blood pressure through the arterial baroreceptor reflexes (Fig. 14). Bulbospinal catecholaminergic and serotonergic path-

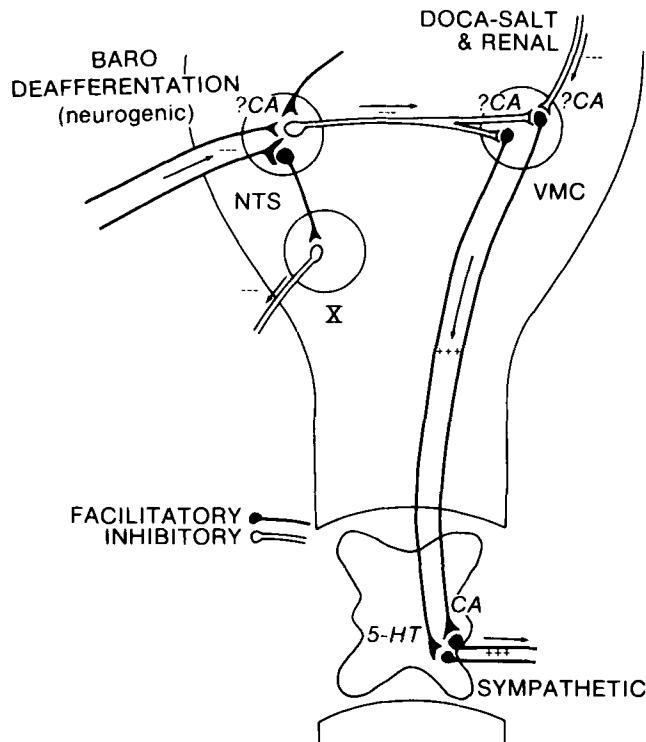


FIG. 14. Excitatory neurons of vasomotor center (VMC) in brain stem [catecholaminergic (CA) or serotonergic (5-HT)] may stimulate preganglionic neurons in IML to increase sympathetic activity and cause hypertension. Normally inhibited, these neurons are disinhibited by 1) decreased activity of inhibitory central CA nerves to VMC as in DOCA-salt or renal hypertension, 2) decreased activity of arterial baroreceptor nerve or other central CA nerves to NTS, or 3) decreased activity of inhibitory CA nerves between NTS and VMC. [From Chalmers (101), by permission of the American Heart Association.]

ways are excitatory and cause an increased preganglionic sympathetic neuronal activity from the intramediolateral horn. This peripheral sympathoadrenal pathway helps to maintain normal arterial pressure, and its ablation causes significant hypotension (167, 168). In contrast the catecholaminergic neurons in the brain stem inhibit the bulbospinal excitatory pathways. The hypertension with NTS injections of 6-hydroxydopamine (178) and the selective decreased norepinephrine turnover in central neurons in the medulla contrasted with increased norepinephrine turnover in peripheral neurons in deoxycorticosterone acetate (DOCA)-salt hypertensive rats suggest this (168, 262, 474). Therefore the relationship between central and peripheral noradrenergic activity appears reciprocal. Central adrenergic neurons may excite neurons in the NTS or inhibit neurons in the lateral reticular nucleus and in the excitatory bulbospinal tracts, reducing peripheral sympathetic activity. Conversely, decreased central norepinephrine activity disinhibits the excitatory bulbospinal tracts, increasing peripheral sympathetic activity and arterial pressure (103, 262).

The facilitation of the baroreflex with clonidine, a central α_2 -adrenergic agonist (181, 583), and its inhibition with angiotensin (208, 227, 601) may be related to the reciprocal effects of the two drugs on central catecholaminergic neurons. The disinhibition of bulbospinal noradrenergic and serotonergic fibers by deafferentation of arterial baroreceptors (neurogenic hypertension) or by decreased activity of inhibitory catecholaminergic nerves in the brain stem (e.g., in DOCA-salt) is significant in the pathogenesis of these two types of experimental hypertension (168, 471). Central noradrenergic nerves are important also in the development and maintenance of renal hypertension (391). Their participation in genetic hypertension, however, is not yet established. They may be involved in the development and triggering of hypertension but not in its maintenance (211, 262).

Propranolol like clonidine may lower blood pressure through a CNS action. Propranolol (which blocks β -receptors) inhibits sympathetic drive and may restore baroreceptor sensitivity in hypertensive states (165, 185, 603). Similarly, during low sodium intake, CNS concentration of norepinephrine increases; this may contribute to central inhibition of sympathetic activity and discharge (82).

Apparently central serotonergic nerves are also significant in the regulation of arterial blood pressure. The activity of bulbospinal serotonergic nerves seems to facilitate the maintenance of arterial pressure in normal animals and the pressure increase in experimental neurogenic hypertension, although this is still controversial (73, 675).

Sole et al. (590) found that serotonin decreases in the medulla and posterior hypothalamus during coronary occlusion in rats. The decrease is selective and blocked by topically applied lidocaine on the left ventricle. These results suggest that serotonergic neurons are involved in the reflex hypotension and bradycardia caused by activation of ventricular afferents.

DOPAMINE. Dopamine receptors at presynaptic sites may inhibit the release of norepinephrine in response to sympathetic stimulation (381, 413). For example, bromocriptine and lergotrile, two dopamine-receptor agonists, significantly impair the renal vasoconstrictor effects and the positive chronotropic effects of cardiac sympathetic nerve stimulation (410, 411). Administering these agonists to animals treated previously with a dopamine-receptor antagonist (pimozide or sulpiride) did not alter the response to nerve stimulation (410). On the other hand bromocriptine and lergotrile given into the ventricular system apparently have minimal effects on arterial pressure or heart rate. Bromocriptine, for example, given intravenously caused more hypotension and bradycardia than when given intravertebrally or into the cerebral ventricles. Both of these compounds have significant neuroendocrinological actions (109), such as the suppression of prolactin secretion and antiparkinsonian effects

through central dopaminergic receptors, but their central cardiovascular effects are not as prominent. Their major cardiovascular site of action appears to be on peripheral prejunctional receptors and sympathetic ganglia causing vasodilatation, bradycardia, and decreased norepinephrine release from nerve terminals. The effect of dopamine on postjunctional receptors is mediated through α -, β -, and dopaminergic receptors.

VENTILATORY RESPONSES TO CATECHOLAMINES. The catecholamines norepinephrine, isoproterenol, and dopamine have significant effects on respiratory drive, particularly during hypoxia. Whereas norepinephrine and isoproterenol augment the hyperventilatory drive during hypoxia in humans (285), dopamine depresses it (670). These interactions are described in more detail in *Reflexes Originating From Chemoreceptor Stimulation*, p. 699.

CARDIOVASCULAR REFLEXES THAT MIGHT INTERACT

This section briefly reviews the specific groups of sensory endings that are the afferent limbs of cardiovascular reflexes and indicates the mechanisms for their activation and some of the reflex responses they mediate when studied in isolation (i.e., the influence of other reflexes eliminated or minimized). The review is not exhaustive, and when possible we refer to recent extensive reviews for additional information.

Sinoaortic Baroreflexes

The determinants of the arterial baroreceptor discharge and of the reflex effects they mediate have been extensively and recently reviewed by Kirchheim (347) and Brown (85). The carotid sinus is the segmental enlargement of the internal carotid artery as it branches from the common carotid artery. The carotid sinus baroreceptor afferent fibers travel in the carotid sinus nerve, which is a branch of the glossopharyngeal nerve. Aortic baroreceptor afferent fibers come from endings in the aortic arch that travel as a separate nerve in the rabbit and guinea pig, while in the dog and cat they travel in the sheath with the vagal and cervical sympathetic nerves. In these latter species, most of the aortic baroreceptor fibers can be identified as separate nerves running within the vagal sheaths at a point just caudal to the nodose ganglion. A few aortic baroreceptor fibers do not join these cervical aortic nerves but instead traverse the vagal nerves (315). The functional importance of these few aortic baroreceptor fibers is uncertain.

The primary baroreceptor endings in the carotid sinus and aortic arch areas are located mainly in the adventitia and superficial media and are subserved by both myelinated and nonmyelinated afferent fibers (85, 210). These sensory endings are transducers of mechanical deformation, and it is the pressure-induced

deformation of the vessel wall and thus of the endings rather than the pressure itself that determines the discharge frequency of the baroreceptors. When the pressure in the carotid sinus is slowly raised from 0 mmHg, the carotid baroreceptors with myelinated afferent fibers begin to fire at a threshold pressure of 40–70 mmHg in most species. From ~75 mmHg to 150 mmHg, discharge of these myelinated baroreceptors increases fairly linearly. In dogs these endings begin to approach saturation at 175 mmHg and by 200 mmHg are fully saturated; i.e., they have reached their maximal frequency. Like all mechanoreceptors the stimulus to these arterial baroreceptors has static and dynamic components, which have important influences on their discharge frequency (85). Two major mechanisms increase total baroreceptor input over the depressor nerves: an increase in the discharge of the individual endings as pressure increases and the recruitment of previously silent fibers as the pressure exceeds their threshold for activation.

Generally the aortic baroreceptors behave as the carotid baroreceptors except that in the dog the aortic baroreceptors may have a higher threshold but a greater sensitivity in the upper pressure ranges and a saturation pressure that is similar to the carotid baroreceptors (181, 498). The differences between carotid and aortic baroreceptors is somewhat controversial (315). In the rabbit, in contrast to the dog, the carotid and aortic baroreflexes appear equipotent and of similar sensitivities (255), while in the rat aortic baroreceptors are clearly dominant (372). These differences in the baroreceptors or their reflexes may be functionally important and may help explain differences in reflex responses among species.

Arterial baroreceptors with nonmyelinated afferent fibers have higher threshold and saturation pressures and lower sensitivities and maximum discharge frequencies than those with myelinated afferent fibers (635, 638). Because of these characteristics their role in the reflex control of the circulation under normal circumstances is uncertain, although they may play a larger role in the reflex control of the circulation in hypertensive states (327) or when circulating catecholamine levels are high (27).

Activating the isolated carotid or aortic baroreceptors results in reflex bradycardia, hypotension, and vasodilatation in most vascular beds. Although cardiac slowing is mediated mainly through activation of cardiac vagal motor neurons, it is also mediated in part by withdrawal of sympathetic outflow to the heart (347). Evidence suggests that myelinated baroreceptors mainly mediate this withdrawal, while both myelinated and nonmyelinated baroreceptors can mediate augmented vagal influences (336). The peripheral vasodilatation is primarily the result of withdrawal of noradrenergic sympathetic outflow to virtually every vascular bed that has been studied, including the kidney, gut, skeletal muscle, spleen, etc., although the autoregulatory responses of this organ largely override

the effects in the kidney (347). Activating cholinergic (607) or histaminergic (50, 79) pathways may facilitate vasodilatation in certain vascular beds, but their role during baroreceptor stimulation is still equivocal. The hypotension is the result of both cardiac slowing (reduced cardiac output) and peripheral vasodilatation. Withdrawing sympathetic outflow to the heart also decreases myocardial contractility (242), which is further accentuated by activation of vagal efferent fibers to the ventricle (389).

Inhibiting the discharge of sinoaortic baroreceptors leads to changes the opposite of those outlined for activating these endings. Thus sinoaortic hypotension increases sympathetic outflow to the heart and peripheral circulation and causes withdrawal of parasympathetic outflow to the heart, resulting in tachycardia and vasoconstriction. The magnitude of the influence of the sympathetic nerves on contractility during bilateral carotid occlusion is modest in conscious dogs (654). The reflex responses to changing baroreceptor input attempt to maintain arterial pressure near the normal set point.

The arterial baroreceptor reflexes are also importantly involved in the reflex regulation of renin secretion (144, 321) and in the regulation of vasopressin secretion (244, 572, 573, 575, 624). Vasopressin and the renin-angiotensin system can play an important role in regulating arterial pressure and vascular resistance. Thus humoral factors under baroreflex control become important components of the overall response.

Activating arterial baroreceptors may suppress ventilation by inhibiting medullary respiratory neurons. In addition to their cardiovascular and respiratory effects, arterial baroreceptors may reflexly decrease skeletal muscle tone, reduce efferent firing to muscle spindles, and reduce the activity of cortical pyramidal tract neurons.

Cardiac Receptors With Afferent Vagal Fibers

The characteristics of sensory endings in the heart have been extensively investigated. Recent reviews by Paintal (492), Coleridge, Coleridge, and Kidd (114, 121), Thorén and Jones (632, 635), Linden (392), Aboud et al. (12, 14), and Donald and Shepherd (182) have summarized much of these data. The International Symposium on Cardiac Receptors of 1976 also provided an excellent overview of this area (264).

The sensory endings in the heart with afferent vagal fibers have been divided into two groups on the basis of the presence or absence of myelination. Thus one group is subserved by myelinated afferent fibers and the other by unmyelinated fibers (C fibers).

The myelinated type A and type B receptors are located in the atria and are called atrial mechanoreceptors. The type B receptors are located mainly at the junction between the great veins and the atria. They appear to respond to increases in cardiac volume

and discharge during the V wave and are little influenced by changes in contractility (492, 519). The type A receptors, activated mainly during atrial systole, are influenced by changes in cardiac volume but to a lesser degree than the type B receptors, increase their discharge significantly in response to positive inotropic interventions, and clearly depend on cardiac rate for their average discharge frequency (492, 518, 519). Receptors with intermediate behavior (features of both types A and B) have also been described. Moreover receptors with a type A discharge pattern can be converted to an intermediate pattern of discharge with volume expansion (335, 518). The endings that exhibit type A and B patterns of discharge apparently behave essentially the same *in situ* in atrial strips (42), suggesting that the differences in the patterns of discharge are a result of the anatomical location of the endings or the way the ending is deformed. Several investigators (121, 256, 489) have made recordings from ventricular receptors with myelinated vagal afferents. There are fewer ventricular myelinated mechanoreceptors than atrial counterparts. Found in both the right (120, 489) and left (120, 256) ventricles, they generally have pulse-synchronous discharge under basal conditions, and their afferent fibers have conduction velocities in the lower range for myelinated fibers [4.6–15 m/s (256)]. Cardiac distension increases the discharge of left ventricular endings (120, 256, 489), which correlates linearly with filling pressure (256) and is increased or reduced by agents that increase or decrease cardiac contractility, respectively (256). Many of these endings are located in or near the endocardium (120, 256). The role of ventricular myelinated mechanoreceptors in circulatory control remains uninvestigated.

Although the behavior of cardiac receptors with myelinated afferent fibers has been studied for some time, only in the last 15 years have we begun to understand the behavior of unmyelinated sensory endings. The conduction velocity of these unmyelinated fibers is less than 2.5 m/s, and they are called C fibers (232). There appear to be two types of cardiac C fibers. The first is activated mainly by irritant substances such as veratridine, capsaicin, nicotine, and phenyl biguanide but is relatively insensitive to mechanical stimuli. The other large group of endings is responsive mainly to mechanical stimuli (45, 634). These mechanoreceptors are located throughout the ventricles and atria, but the left ventricle is more profusely innervated than the right (45). They have a sparse irregular discharge under resting conditions in both open-chest (634) and closed-chest (spontaneously breathing) animals (618). Mechanoreceptor C fibers in the atria apparently increase their discharge in response to cardiac volume changes, as reflected in atrial transmural pressure (618). Volume expansion or increased negative intrathoracic pressure augments the discharge of these atrial C fibers (618). Changes in contractility or heart rate do not significantly affect atrial C fibers (513). Left ventricular mechanoreceptor C

fibers are mainly epicardial (45, 256, 584, 633). Many other C fibers subserve endings in the left and right ventricles (618, 633). The mechanical contraction of the left ventricle appears to activate these endings, but their discharge frequency, once activated, seems to be determined mainly by the end-diastolic pressure and thus volume (618, 633). Positive inotropic agents increase the discharge of these endings (472, 584, 633); agents that reduce ventricular contractility reduce it (614, 633). Thus changes in cardiac volume may have an important influence on C fibers in both the atria and the ventricles.

The relative importance of receptors with myelinated fibers as opposed to those with C fibers in the mediation of reflex inhibitory responses has been somewhat controversial (634). Although evidence suggests that the inhibitory influence mediated by cardiac receptors is mainly of C-fiber origin (634), recent studies (380) show that the inhibitory responses to distension of the venoatrial junctions may be the result of activation of atrial receptors with myelinated afferent fibers. Regardless of the exact source of the inhibitory influence, receptors in the atria and ventricles with afferent vagal fibers clearly exert a tonic inhibitory influence on the vasomotor centers (422), which hemorrhage, vagal cold block, vagotomy, or epicardial application of local anesthetic can reduce or eliminate. The tonic inhibitory influence of vagal afferent input on sympathetic outflow to different regional circulations is not uniform (5, 14). The sensory endings in the atria, ventricles, and lungs may each contribute to this influence (421). Cardiac vagal afferent fibers appear to exert their largest inhibitory influence on sympathetic outflow to the kidney and splanchnic circulation with smaller influences on sympathetic outflow to skeletal muscle (499, 671). When volume expansion (623), aortic occlusion (434), coronary occlusion (616), or intracoronary or epicardial acetylstrophantidin augment the activity of cardiopulmonary vagal afferent fibers (613, 626), the inhibitory influence of these receptors is augmented. Like the arterial baroreceptors, cardiac receptors with afferent vagal fibers are also important in the reflex regulation of renin secretion (391, 421, 422, 434, 472, 499, 612, 613, 616, 619, 623, 626, 627, 685) and vasopressin secretion (623, 624).

In addition to these inhibitory influences atrial receptors may mediate increases in heart rate during volume expansion or during distension of the venoatrial junctions (390). Apparently the tachycardia is mediated mainly by increases in sympathetic outflow to the sinus node without evidence for a significant increase in sympathetic influence on the ventricles (390).

Cardiac Receptors With Afferent Sympathetic Fibers

A large population of sensory endings in the atria and ventricles have spinal afferent fibers, which travel with the cardiac sympathetic nerves to the spinal cord.

They have been called cardiac sympathetic afferent fibers (420). Although the increased discharge of these endings during coronary artery occlusion have been widely investigated (72, 420, 645), their physiological behavior has not been as intensively and systematically investigated as that of the vagal endings. The determinants of sympathetic afferent discharge appear similar to those of afferent vagal fibers (72, 286, 369, 420, 512, 645). Some sympathetic afferent endings have myelinated and others nonmyelinated fibers (418). In contrast to afferent vagal fibers, many sympathetic afferent fibers are probably activated by both chemical (e.g., bradykinin) and mechanical stimuli (418).

No evidence indicates that these sensory endings exert important tonic influences (excitatory or inhibitory) on sympathetic outflow or cardiac vagal motor outflow. On the other hand activating these afferent fibers seems to result either in inhibitory or excitatory responses, depending on the technique of activation and the intensity of the stimulus. Thus, stimulating sympathetic afferent fibers can result in decreases in renal nerve activity with low-intensity electrical stimulation and increases in activity with high-intensity electrical stimulation (511, 665). Activating sympathetic afferent fibers alters the discharge of sympathetic outflow to several vascular beds, but few studies have examined their influence on sympathetic outflow to the heart (418). Activating sympathetic afferent fibers can inhibit the discharge of cardiac vagal motor neurons (569).

Activating these sensory endings with coronary artery occlusion in spinal animals mediates clear excitatory reflex responses, particularly reflex excitation of cardiac sympathetic efferent nerve activity (86, 206, 419). The reflex response of efferent cardiac sympathetic nerves to coronary occlusion mediated by sympathetic afferents, which have been observed when the spinal cord is sectioned, has been reported to be apparent no longer when the spinal cord is intact (206), although this remains an area of debate. Led-some and Kan (384) suggest that these sympathetic afferent fibers are the principal pathway for cardiac pain. Many of the responses to these activated endings in conscious animals and humans may be the result of activating higher cerebral centers rather than the result of activating spinal reflexes or even more classic brain stem vasomotor centers. Input from cardiac sympathetic afferent fibers converges with input from forelimb somatic receptors in the cord (221) on interneurons, which may account for the referred shoulder and arm pain during myocardial ischemia or infarction.

Reflexes Originating From Chemoreceptor Stimulation

The chemoreceptors are sensors in the carotid and aortic bodies that are excited by reductions in arterial P_{O_2} , increases in P_{CO_2} , and decreases in pH. They

provide an important control system for oxygen conservation and may be activated by various chemicals (e.g., lobeline, phenyl biguanide, nicotine, capsaicin, cyanide).

The carotid bodies are two small structures situated at the bifurcation of the common carotid arteries; the aortic bodies are distributed along the aortic arch. Both structures are very vascular. The occipital and ascending pharyngeal arteries supply the carotid bodies, whereas the aortic bodies receive their supply from small branches of neighboring vessels, including the left coronary artery (117, 118, 191, 320). The carotid and aortic bodies have similar structures and include specialized cells, the gloma type I cells, which release catecholamines that may modulate the activity of the sensory endings (349).

CENTRAL PROJECTION. The chemoreceptor afferents travel with the baroreceptor afferents in the glossopharyngeal and vagal nerves to the medulla and relay in the NTS, where the terminals from the two types of afferents may be closely integrated (136, 303, 368, 467). From the first synapse in the NTS, projections to the vagal preganglionic neurons and to other excitatory neurons in the reticular formation mediate the respiratory and cardiovascular responses.

RESPONSES. The major responses to chemoreceptor stimulation are reflex bradycardia (which is predominantly vagal), hyperventilation, and vasoconstriction (156–158, 159, 362, 367). The bradycardia provides a protective stimulus to reduce myocardial oxygen demand, and the hyperventilation increases oxygen delivery and reduces hypercapnia. Hyperventilation, which might be either reflex or central in origin, opposes the reflex bradycardia and can either reduce it or prevent it (54). Hyperventilation also opposes the vasoconstrictor responses (129, 159, 163, 274, 281, 366, 368, 546).

The local vascular effects of hypoxia and acidosis are inhibitory and may cause vasodilatation and hypotension (280, 281, 283, 359). On the other hand arterial pressure is maintained during hypoxia because of reflex vasoconstriction through activation of chemoreceptors (129, 274, 281, 359, 366, 368, 546). Chemoreceptors may reflexly increase arterial blood pressure and cause a redistribution of blood flow through selective vasoconstriction (53, 55, 96, 258, 282, 360).

Lugliani et al. (417) examined the response to hypoxia in humans. In normal subjects arterial pressure was maintained or increased during hypoxia, whereas in subjects who had undergone resection of the carotid bodies arterial pressure decreased significantly. Experiments in animals also indicate that the increase in arterial pressure during stimulation of chemoreceptors is related primarily to an increase in peripheral vascular resistance predominantly in the renal, muscle, and splanchnic beds (54, 96, 156–159, 281, 360, 362, 367).

The carotid bodies have a much more potent effect on respiration than the aortic bodies (128, 160, 563). Consequently their relative effects on the cardiovascular responses reportedly differ, probably as a result of interactions between the respiratory and cardiovascular reflexes (129, 274, 366, 368, 546). If artificial ventilation eliminates ventilatory responses, then cardiovascular responses of the carotid and aortic chemoreceptor stimulation are more comparable (160). Our group contrasted the cardiovascular responses of aortic and carotid chemoreceptors using nicotine and cyanide as stimuli and found that the magnitude of bradycardia was greater during carotid stimulation (96). Others also have shown that the reflex bradycardia originating in the carotid chemoreceptors is more pronounced than that of the aortic chemoreceptors (33, 340). With respect to the inotropic effect, Stern and Rapaport (595) reported that stimulating aortic bodies with nicotine promptly increased rate and left ventricular contractility. In contrast, ventricular contractility declined during carotid hypoxia but only when the vagi were intact (169). Downing et al. (184) confirmed a similar decline in atrial and ventricular contractility of the paced heart of the dog during carotid hypoxia; however, the fall in ventricular contractility persisted after vagotomy, probably because sympathetic tone was withdrawn.

Thus the carotid chemoreceptors are more potent

in inducing bradycardia and hyperventilation than the aortic chemoreceptors. Debate continues about the inotropic responses to chemoreceptor stimulation.

SELECTIVITY OF VASCULAR RESPONSES. Although most vascular beds constrict when chemoreceptors are stimulated, some dilate (53, 55, 96, 156–159, 258, 282, 360, 362, 367). Vasodilatation is seen in the extremities, mostly in the cutaneous bed (53, 96, 281, 367, 500) and in the coronary bed (258) (Figs. 15, 16). The coronary dilatation, evident even when changes in contractility were minimized, was associated with a small increase in coronary sinus P_{O_2} (258). It is neurogenically mediated through vagal efferent fibers and can be blocked by atropine (258).

The effect of chemoreceptor stimulation on cerebral blood flow is negligible. We have not been able to demonstrate the reflex vasodilator response in cerebral vessels during chemoreceptor stimulation suggested by others (282, 507); local vasodilator mechanisms seem sufficient to account for cerebral vasodilatation during systemic hypoxia, and a contribution from a vasodilator chemoreceptor reflex appears unnecessary (282, 360).

The differential neurogenic reflex responses with vasoconstriction in muscle and kidney and vasodilatation in coronary vessels add an important mechanism for redistribution of blood flow to organs with

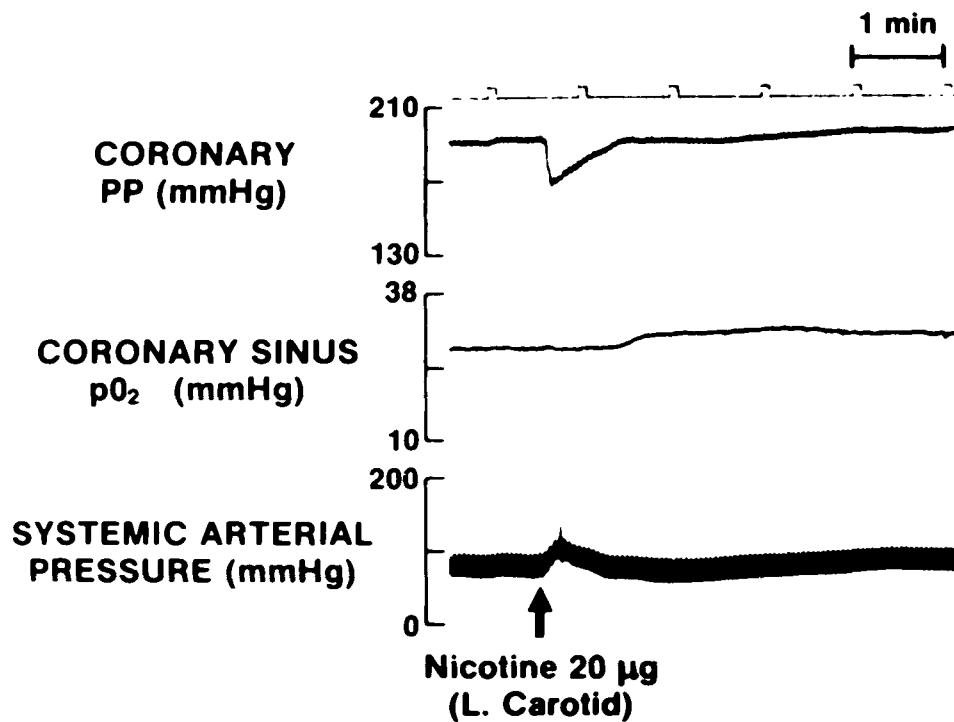


FIG. 15. Stimulation of the carotid chemoreceptors with nicotine causes a reflex fall in coronary perfusion pressure (PP) and coronary vasodilatation during constant cardiac pacing and constant coronary blood flow (perfusion pump). Dilatation is not metabolic in view of the rise in coronary sinus O_2 pressure (P_{O_2}). Atropine and vagotomy partially block it. [From Heistad and Abboud (274), by permission of the American Heart Association.]

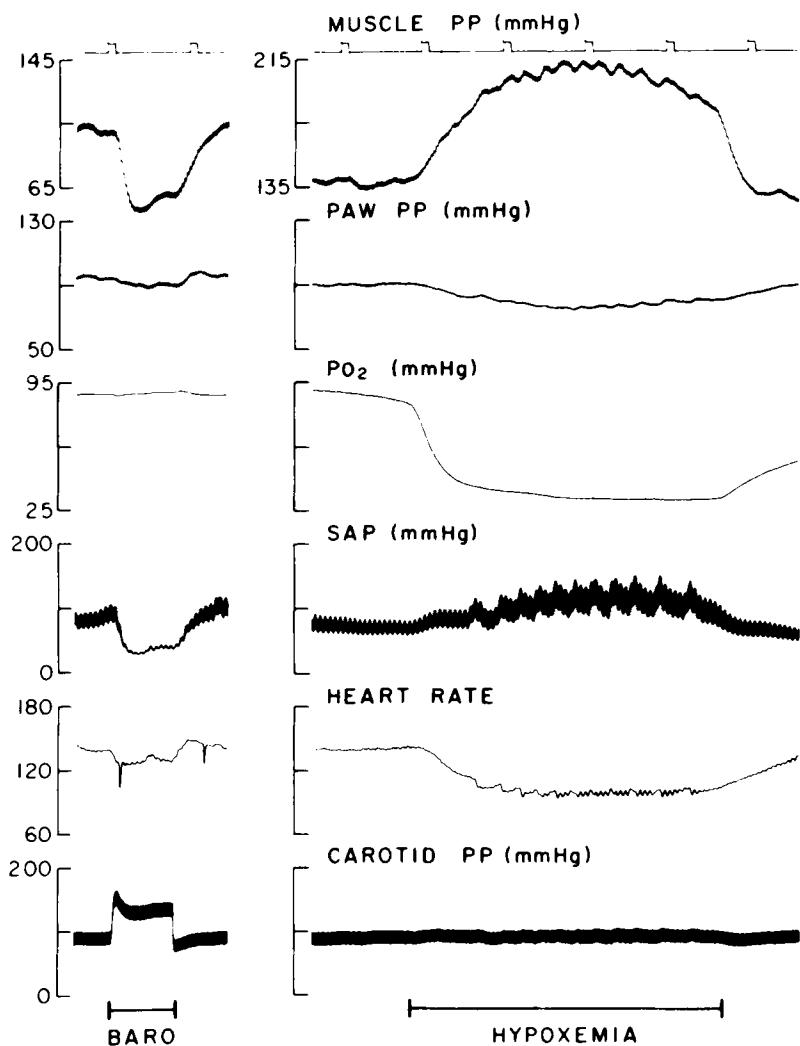


FIG. 16. Activating carotid chemoreceptors by carotid hypoxemia causes hypertension, bradycardia, and reflex vasodilatation in paw and constriction in muscle. Paw and muscle perfused separately at constant blood flow. Carotid baroreceptor stimulation (BARO) in contrast causes hypotension, bradycardia, and vasodilatation in muscle and paw. SAP, systemic arterial pressure. [From Abboud et al. (11) and Heistad, Abboud, et al. (281).]

high metabolic requirements. This effect in addition to the local metabolic vasodilatation facilitates effective oxygen distribution in hypoxic states.

SUPPRESSION OF CARDIOVASCULAR EFFECTS: HYPERVENTILATION. Stimulating pulmonary stretch receptors significantly alters the vasoconstrictor response to chemoreceptor stimulation in skeletal muscle, mesenteric, and renal beds (156, 281, 546). Hyperventilation not only attenuates but sometimes reverses the constrictor response in these vessels. The same is true of the reflex bradycardia (54, 129). Thus, in examining the integrated cardiovascular response to hypoxia, the interaction of the arterial chemoreceptors and pulmonary stretch receptors should be considered (366, 368).

The mechanisms involved in the hyperventilatory interaction have been addressed recently (153). They include increased activity of the respiratory centers, a pulmonary vagal inflation reflex, and a fall in arterial PCO₂ (149, 151). Not only do they all cause tachycardia and vasodilatation, but they effectively inhibit the

reflex bradycardia and vasoconstriction of carotid chemoreceptor origin.

POTENTIATION OF RESPONSES. The magnitude of the response to chemoreceptor stimulation may be modified by several factors that often work together to effectuate a strong circulatory adjustment. Three interventions can potentiate the chemoreceptor drive during hypoxia: 1) acidosis, 2) catecholamines, and 3) systemic hypotension.

Acidosis and hypercapnia increase arterial pressure much more during carotid hypoxia than during normoxia. The increase appears greater than the additive effect of the three stimuli (502).

Catecholamines, particularly norepinephrine, produce hyperventilation in animals and humans (142, 285, 661). The response to norepinephrine and isoproterenol is significantly greater in humans when they are hypoxic than when they are normoxic (142, 285). Suppressing the chemoreceptor drive with 100% oxygen reduces the response to norepinephrine. Propranolol also blocks the response to norepinephrine and

isoproterenol, even in the presence of hypoxia (285). Thus it appears that stimulation of β -adrenergic receptors may augment the chemoreceptor response to hypoxia. Norepinephrine, which is in the glomus cells of the carotid body, may sensitize the afferent nerve terminals of the chemoreceptors. Wasserman et al. (661, 662) suggested that isoproterenol increases ventilation through an additional mechanism independent of peripheral chemoreceptors. They propose that central chemoreceptor drive is enhanced by increases in PCO_2 associated with the sudden increase in cardiac output and reduced ventilation/perfusion ratio (\dot{V}_A/\dot{Q}). The increase in ventilation persists after denervation of carotid and aortic chemoreceptors and after bilateral vagotomy. Increasing cardiac output by pacing alone may increase ventilation (661).

Recent studies indicate that decreases in systemic arterial pressure augment the chemoreceptor reflex. This interaction between arterial baroreceptor input and chemoreceptor input is important because hypotension in intact animals and patients often occurs simultaneously with hypoxia, acidosis, and hypercapnia (15, 277, 278). This interaction is discussed in **MODIFYING REFLEX GAIN BY CHANGING TONIC INFLUENCE OF ONE SET OF SENSORY AFFERENTS**, p. 713.

DEPRESSION OF RESPONSE: DOPAMINE. Recent observations indicate that dopamine, another catecholamine in the glomus type I cell of the carotid body, may suppress chemoreceptor drive (440, 466, 549, 551), although some studies report that in the dog dopamine stimulates ventilation (66, 317). Welsh, Heistad, and Abboud (670) reported a significant suppression of the hyperventilatory response to hypoxia by intravenous infusion of dopamine in humans [Fig. 17; (274)]. The results are compatible with the hypothesis (448) that when hypoxia activates afferent nerves in the carotid body, dopamine is released from type I cells. Dopamine may then suppress the magnitude of afferent chemoreceptor discharge at the nerve terminal.

An alternative theory (486) suggests that a contin-

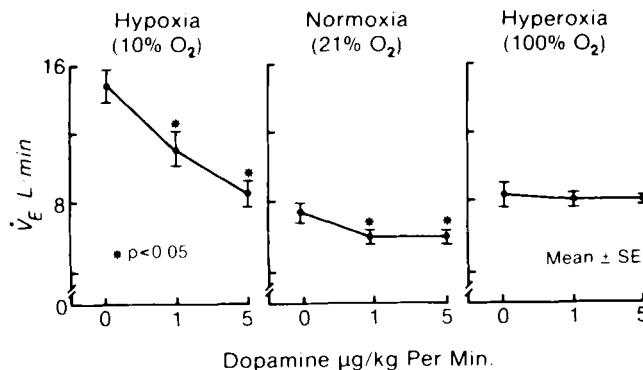


FIG. 17. Dopamine (1 and 5 $\mu\text{g}/\text{kg}^{-1}/\text{min}$) suppresses hyperventilatory response (\dot{V}_E) to hypoxia (10% O_2) in humans. Minimal suppression during normoxia; none during hyperoxia, suggesting chemoreceptor mediation of dopamine action. [From Heistad and Abboud (274), by permission of the American Heart Association.]

uous secretion of dopamine in the carotid body reduces the discharge rate of chemoreceptor fibers and that reduction in dopamine secretion during hypoxia increases neural discharge.

The response to dopamine during hypoxia, regardless of the mechanism, may have important clinical implications. Dopamine may, for example, decrease ventilation in clinical shock states.

Thus, whereas norepinephrine and isoproterenol increase ventilation, dopamine decreases ventilation, particularly during exposure to hypoxia. Both neurotransmitters may be physiologically important modulators of chemoreceptor functions because they mediate a reciprocal function. A similar reciprocal function between norepinephrine and dopamine has been proposed in other parts of the CNS (40).

COMPARISON OF RESPONSES TO BARORECEPTOR AND CHEMORECEPTOR NERVE STIMULATION. The possibility that injections of chemicals in the region of the carotid body might also activate baroreceptor and other endings has to be considered. Several studies negate that possibility, indicating that the chemicals produce their effects independently of baroreceptors and primarily through chemoreceptors (318, 319, 490). Although the responses to stimulation of chemo- and baroreceptors may include hypotension, bradycardia, and vasodilatation in the paw, stimulating the chemoreceptors alone causes marked vasoconstriction in muscle and vasodilatation in paw, whereas stimulation of baroreceptor nerves causes vasodilatation in both muscle and paw (96). Furthermore, during maximal electrical stimulation of the baroreceptor nerves, the superimposition of the chemical stimulus to the chemoreceptors reverses the vasodilatation in muscle, produces significant vasoconstriction, and potentiates the vasodilatation in paw [Fig. 18; (96)]. These findings demonstrate two points. One is that simultaneous stimulation of chemoreceptors and baroreceptors can cause vasoconstriction. The second is that the vasodilatation induced by chemoreceptor stimulation in the paw is greater than can be expected from simple withdrawal of sympathetic vasoconstrictor drive (which was already withdrawn from baroreceptor stimulation), suggesting activation of a vasodilator system.

CHEMORECEPTOR MEDIATION OF SUSTAINED AND PROLONGED STIMULATION OF RESPIRATION BY CENTRAL NEURAL MECHANISM. Recent studies by Millhorn et al. (460) indicate that stimulating carotid chemoreceptor afferents in both cerebrate and decerebrate cats causes a sustained increase in respiratory activity that long outlasts the direct effects of the stimulus on chemoreceptors. This effect is different from what had been described as the respiratory-after-discharge phenomenon (192). The enhancement of respiratory activity lasted the 90 min of follow-up and could not be reproduced by stimulating other afferents, such as somatic afferents, or by hypercapnic

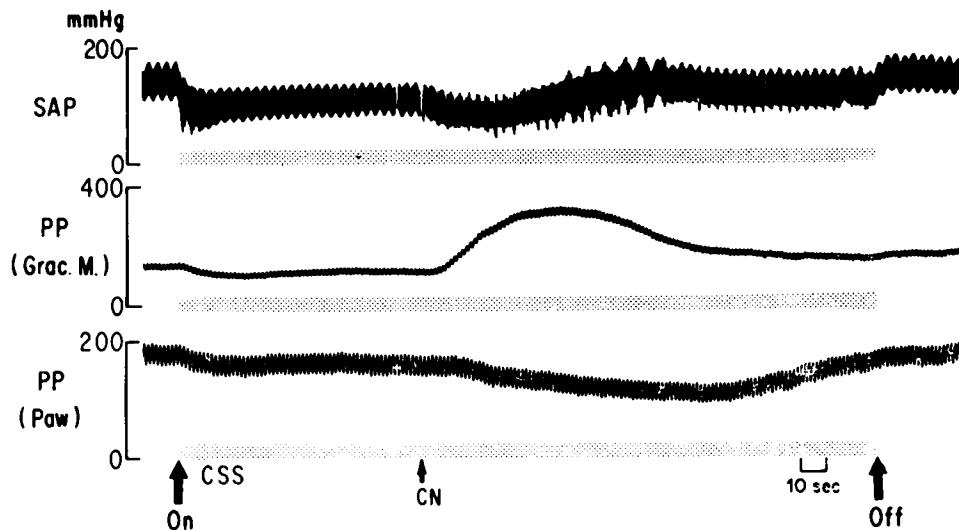


FIG. 18. Blood flow to gracilis muscle (Grac. M.) and paw maintained constant with pump. During sustained stimulation of carotid sinus nerve (CSS), close to bulb to exclusively activate baroreceptor nerves, withdrawal of sympathetic tone caused reflex hypotension and dilatation in muscle and paw. Cyanide (CN) injected into ascending aorta during electrical stimulation of baroreceptors activated chemoreceptors, causing vasoconstriction in muscle and further dilatation in paw. [From Calvelo, Abboud, et al. (96), by permission of the American Heart Association.]

stimulation of central chemoreceptors [Fig. 19; (460, 461)]. It appears caused by activation of an endogenous central serotonergic mechanism that facilitates respiration (461). The gradual activation of this system by carotid chemoreceptors and its long lasting effect may explain the sustained increase in ventilation during acclimatization to high-altitude hypoxia.

Reflexes Originating in Lung

Coleridge and Coleridge (112) recently have reviewed vagal and sympathetic pulmonary afferents that may play a role in circulatory control. They describe three categories of vagal afferent endings: baroreceptors in major arterial branches, slowly adapting stretch receptors activated during lung inflation, and C-fiber endings that signal pressure changes downstream from the pulmonary resistance vessels. Various chemicals, such as capsaicin, bradykinin, and prostaglandins may also stimulate the vagal C fibers, but the presence of vagal nerve endings that function as pulmonary chemoreceptors responsive to changes in P_{O_2} , P_{CO_2} , and pH in the pulmonary arterial blood is still a matter of debate.

Table 1 summarizes the pulmonary receptors, their afferents, the stimuli that provoke them, and the responses.

PULMONARY ARTERIAL BARORECEPTORS. Coleridge and Kidd (125-127) indicate that these receptors are distributed predominantly in the branches of the pulmonary artery, are active at normal pulmonary arterial pressure, and have a discharge pattern that resembles that of arterial baroreceptors and reaches a maximum discharge frequency of 20-30 impulses/cycle.

The impulses travel in A δ -fibers. Several similar endings have been located within the lung (125). Bradycardia sometimes accompanies the reflex depressor effects caused by moderate distension of the right pulmonary artery, especially if the sinoaortic baroreceptors are denervated. Vagotomy abolishes these effects. Others (42, 232) have observed similar effects.

At high distending pressures (80-100 mmHg) the depressor effect is reversed to a pressor one. Similarly, during a right heart bypass experiment, where venous return is pumped directly into the pulmonary artery and its branches, an increase in pulmonary artery distending pressure increases phrenic nerve activity and increases vascular resistance in the hindlimb without changing renal resistance (384). Vagotomy also abolishes these effects. Krahl (370) has proposed that an aggregation of chemoreceptor cells termed "glomus pulmonale" in or close to the pulmonary artery receives its blood supply directly from the pulmonary artery in adult animals, functions as a mixed venous chemoreceptor, and could be activated by high pulsatile pressure. The aortic chemoreceptors, which are in close proximity to the pulmonary artery, may also actually be stimulated during pulmonary artery distension by pulsatile pressures exceeding 80 mmHg. Such distension may reduce blood flow through the vasa vasorum and activate the glomus cells by hypoxia. Debate continues over the role of these endings as pulmonary chemoreceptors.

SLOWLY ADAPTING STRETCH RECEPTORS: LUNG INFLATION REFLEX. In 1871 Hering showed that inflation of the lungs results in cardiac acceleration. In 1936 Anrep et al. (38) confirmed this. More recently it was shown to be associated with reflex vasodilatation (152, 487).

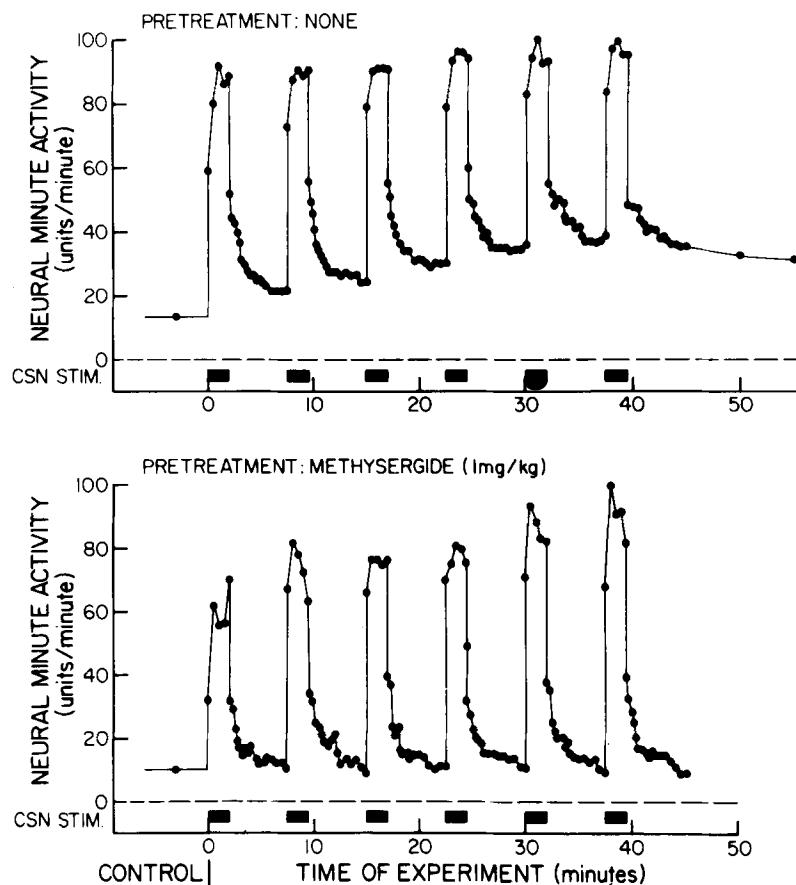


FIG. 19. Repeated brief (2-min) carotid sinus nerve (CSN) stimulations (25 Hz, 0.5 ms, 0.25–1.5 V; *heavy horizontal lines*), resulting in significant increases in phrenic nerve activity that outlast stimulus by up to 5 min of afterdischarge. Also inspiratory activity has long-lasting increase (> 30 min) that becomes progressively larger with each stimulus and is blocked by intravenous methysergide (*lower panel*). Data normalized so highest value during stimulation equals 100 units. Partial CO_2 pressure is 34 mmHg. [From Millhorn et al. (461).]

Weak electrical stimulation of the central cut end of the pulmonary branches of the vagal nerves can mimic these responses (38).

Several groups of investigators (35, 99, 100, 243, 263) reported that inflation of the lungs to pressures of 9 cmH_2O or less causes tachycardia, whereas inflation to 30–40 cmH_2O causes bradycardia.

Slowly adapting receptors with vagal myelinated A fibers are stimulated by low levels of lung inflation (342, 463, 552); therefore they are probably receptors for the reflex tachycardia (38). The more rapidly adapting receptors with A fibers (463) are stimulated by somewhat higher inflation pressures (10–15 cmH_2O) and may contribute to either the reflex tachycardia or bradycardia (342).

Recently Kaufman et al. (342) reported that pulmonary and bronchial receptors with unmyelinated afferent vagal C fibers are also activated by inflation, but the inflation pressures necessary to activate them were higher, averaging 16.4 and 26.5 cmH_2O , respectively. These receptors may be responsible for the reflex bradycardia reported at high lung inflation pressures.

Thus inflation at low pressure activates the classic Hering-Breuer receptors, which are slowly adapting with myelinated vagal A-fiber afferents and cause tachycardia and vasodilatation. Higher inflation pres-

sures activate pulmonary and/or bronchial vagal C fibers with unmyelinated afferents, causing bradycardia and vasodilatation.

The effect of lung inflation on respiration may be one of a negative feedback, but its role in conscious subjects is uncertain, although recently extensively reviewed (333).

The stimulus triggered by inflation and stretch may be modified by several factors, including anesthetics, congestion of the lung, and changes in PCO_2 (112). A fall in alveolar PCO_2 sensitizes the endings to stretch so that at constant total lung volume, afferent activity increases as lung PCO_2 falls (115, 564). This establishes an inhibitory feedback loop that controls hyperventilation.

The tachycardia is caused by withdrawal of vagal efferent activity, is independent of any central inspiratory activity, and occurs even when hypocapnia abolishes central respiratory drive (38, 39). The vasodilatation is caused by reduction in sympathetic vasoconstrictor tone, is not uniform, and is greater in skeletal muscle than in splanchnic and cutaneous beds (155, 240).

The slowly adapting lung inflation reflex tends to partly oppose the effects of chemoreceptor stimulation when an intact animal is rendered hypoxic. Stimulating chemoreceptors causes reflex bradycardia and va-

TABLE 1. Pulmonary Afferents

Receptors	Afferents	Stimulus	Response
Arterial baroreceptors	Vagal A fibers (arterial walls)	Pulmonary arterial distension Normal pressure High pressure*	Bradycardia, hypotension Tachycardia, hypertension, hyper-ventilation, increased hindlimb resistance
Stretch receptors	Vagal A or C fibers (pulmonary and bronchial tissue) Vagal A fibers Vagal C fibers	Lung inflation Low pressure (8–15 cmH ₂ O) High pressure (15–30 cmH ₂ O)	Tachycardia, vasodilatation† Bradycardia, hypotension, vasodila-tation
Primarily chemosensitive receptors	Vagal C fibers J receptors	Bradykinin, prostaglandin Embolii Hyperinflation Anesthetics Increase in venous pressure Congestion Chemicals Hyperinflation Arterial hypertension	Bradycardia, hypotension, vasodilatation, apnea
Mechanosensitive and/or chemosensitive and pain receptors	Sympathetic afferents	Venous hypertension	Tachycardia, hypertension, decreased renal resistance

* May stimulate chemoreceptors. † Predominantly in skeletal muscle.

soconstriction in skeletal muscle, but the increased activity of pulmonary stretch receptors caused by hyperventilation and a reduction in PCO_2 partly suppresses that effect. If PCO_2 is prevented from falling, the tachycardia and vasodilatation produced by lung inflation are less evident (148). The reflex vagal bradycardia and sympathetic vasoconstriction caused by stimulating or unloading baroreceptors, respectively, are suppressed by lung inflation and are fully expressed only during expiration.

PULMONARY AND BRONCHIAL C FIBERS. These afferent unmyelinated vagal C fibers are more widely and densely distributed than the myelinated pulmonary vagal branches. They predominate in pulmonary capillaries or pulmonary veins but may also be present in bronchi (113, 122) and discharge infrequently and irregularly at rest. Their activation, however, increases significantly in response to various exogenous and endogenous chemicals, such as capsaicin and phenyl biguanide on one hand and prostaglandin or bradykinin on the other. Pulmonary emboli, hyperinflation of the lung (342), anesthetics, and stepwise increases in pulmonary venous pressure also appear to stimulate them (113, 116, 122, 123). Their activation causes respiratory and cardiovascular inhibition with bradycardia, apnea, and peripheral vasodilatation. Activation of pulmonary C fibers has also been associated with loss of control of voluntary muscle tone and reflex inhibition of spinal reflexes (152). The interaction between somatic motor function and autonomic afferent pathways and their interdependence are becoming more apparent. Paintal (491) suggested that pulmonary C-fiber endings (J receptors), which mediate the so-called J reflex, are stimulated by pulmonary conges-

tion during severe exercise. The resulting inhibitory reflex of visceral and somatic activity should prevent overexertion.

SYMPATHETIC AFFERENTS. Sympathetic afferents respond to pulmonary arterial hypertension or pulmonary venous distension but with only transient bursts of activity (412, 480). Activating cardiopulmonary sympathetic afferent endings may cause reflex tachycardia and a fall in renal vascular resistance (62, 665); thus they may contribute to the tachycardia and reflex vasodilatation caused by lung inflation. These endings may also resemble cutaneous mechanoreceptors with A_δ-fibers in their sustained response to endogenous chemicals, such as bradykinin applied locally in very small concentrations (112). Thus, when the intensity of stimulation reaches a level that corresponds to the pain threshold, release of endogenous substances may cause a sustained activation of sympathetic afferents and pressor rather than depressor effects.

Reflexes Originating In Skeletal Muscle During Exercise

Numerous investigators have examined the mechanisms of the pressor response, tachycardia, and hyperventilation during static and dynamic exercise described by Alam and Smirk (29) in 1937. Two main components comprise the response to exercise. One is related to central cortical or hypothalamic factors and the other to a somatic reflex originating in the contracting muscle (225, 241, 373, 464, 542).

Receptors in the contracting and possibly ischemic skeletal muscle are activated and trigger reflex sympathetic discharge. Two types of somatic afferent fi-

bers predominate: 1) small, myelinated group III or A_δ-fibers, which transmit activity of ergoreceptors and 2) small, unmyelinated group IV or C fibers, which respond predominantly to chemicals and noxious stimuli (342, 351, 557). Their locations, ultrastructures, and central projections are not well studied.

Kalia et al. (334) traced the muscle afferents into the CNS using the transganglionic transport of horseradish peroxidase. Their findings indicate that the afferents terminate in the dorsal column nuclei and in the NTS and suggest that the first-order afferent fibers from muscle terminate in the major sensory nuclei related to cardiovascular, respiratory, and gastrointestinal control.

Several other studies indicate that an element in the pressor and tachycardic response to exercise depends on central command and is independent of muscle afferents (225, 241, 373, 464, 542). In 1938 Alam and Smirk (29) carried out an experiment in a patient without sensation in one leg (probably with syringomyelia) that confirms the importance of muscle afferents. During ischemic exercise of either the normal or the insensitive leg a pressor response was noted, but when exercise was stopped and ischemia sustained by arterial occlusion the pressor response was absent in the insensitive leg and sustained in the sensitive one (Fig. 20). Recent studies confirm and extend these concepts (224, 542, 544). Experiments in humans with peridural anesthesia suggest that pressor responses to static or dynamic exercise are mediated through sensory endings in the contracting muscle, which are independent of those endings activated by ischemia (224, 542). The pressor response to isometric contraction occurred when anesthetic still blocked the pressor response to muscle ischemia.

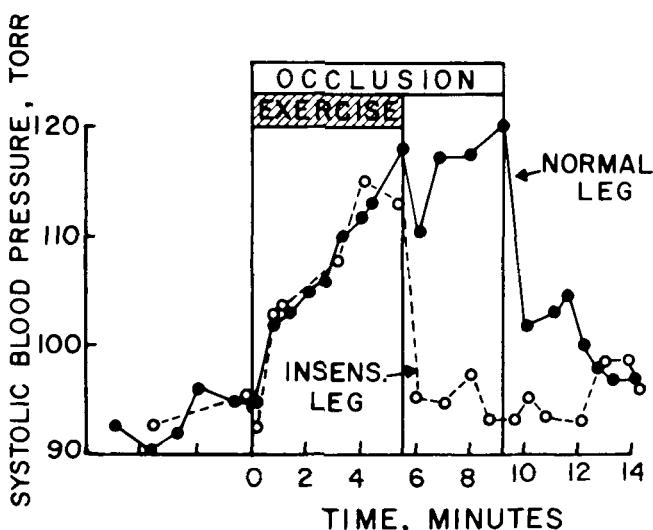


FIG. 20. Pressor responses to ischemic exercise in normal leg (solid line) and insensitive leg (dashed line) were similar. Ischemia of normal leg without exercise sustained pressor response, but ischemia of insensitive leg did not. [From Rowell et al. (542), by permission of the American Heart Association, adapted from Alam and Smirk (29).]

BARORECEPTOR REFLEX DURING EXERCISE. The pressor response to exercise is caused by increased heart rate, cardiac output, and vasoconstriction in the nonexercising muscle and other vascular beds. Thus, despite a significant rise in arterial pressure, vascular resistance and heart rate increase. Activating arterial baroreceptors clearly does not inhibit the excitatory sympathetic drive of the central command or of the somatic reflex. However, the arterial baroreceptors still modulate changes in arterial pressure and heart rate but from a higher base line. Several studies in humans (57, 143, 415) and animals (454, 455, 596) indicate that in general the regulation of arterial pressure and heart rate by baroreceptors is essentially unchanged except for the reflex bradycardia. Isometric handgrip in humans suppresses the reflex bradycardia caused by neck suction (415) or phenylephrine-induced hypertension (143). In one experiment on running dogs the reflex bradycardia during methoxamine-induced hypertension was reduced (445), but in another the reflex response to carotid hypertension was preserved (455). In anesthetized animals, simulating exercise by electrically stimulating ventral spinal nerve roots did not alter the bradycardia caused by a rise in arterial pressure (596). Apparently the excitatory influence of arterial baroreceptors on vagal cardiac inhibitory neurons causing bradycardia may be partly opposed during exercise possibly because of hyperventilation or interaction with central suprabulbar pathways. Possible variations in set point, in responsiveness of the sinus node, and in level of alertness, sedation, or respiration need to be considered in interpreting these interactions.

CARDIOVASCULAR RESPONSES AND BLOOD FLOW DISTRIBUTION. In addition to the marked increase in blood flow to the exercising muscle, tachycardia and increased myocardial contractility increase coronary flow markedly. Whether sympathetic coronary vasoconstriction limits a possibly greater increase in coronary flow during exercise has not been explored systematically.

Leg exercise in humans reflexly reduces in forearm blood flow through sympathetic vasoconstriction (58). In the exercising muscle the accumulation of vasodilator metabolites inhibits the sympathetic vasoconstrictor response (543). This sympatholysis permits maximal vasodilatation in the legs and, as vasoconstriction occurs in the nonexercising muscle, blood flow is beneficially distributed to favor the active muscle and a rise in arterial pressure is maintained to perfuse the active muscle despite the compressive force of muscular contraction. Splanchnic blood flow decreases significantly during exercise despite large increases in cardiac output (540). In addition to vasoconstriction in splanchnic and in the nonworking muscle beds, vessels in the skin and kidney may also constrict and flow redistribution can redistribute a total of ~600 ml of oxygen to the working muscle each minute.

Vasoconstriction in exercising dogs occurs also in the inactive beds, such as the splanchnic or renal bed. However, the constriction may not be severe enough to reduce blood flow. If the animal is in congestive failure or if cardiac output is limited, the vasoconstrictor response reduces flow in these beds and allows a more effective redistribution of the limited cardiac output to the exercising muscle and the myocardium (290).

Several factors are integrated in the final cardiovascular and respiratory response to exercise. We have described input from higher centers and from somatic afferents sensing both mechanical and chemical stimuli in the contracting muscle. Changes in blood gases, which contribute to the vasoconstriction and hyperventilation, also activate chemoreceptors. In a closed-loop system the arterial and cardiopulmonary afferents as well as lung inflation receptors may modulate the ultimate effect of exercise.

Reflexes Originating From Facial and Upper Airway Receptors: Diving Reflex

Activating facial and upper airway receptors primarily by facial immersion in water (simulated diving) triggers the diving reflex. The impulses from this region reach the CNS via the trigeminal afferents and relay in the area of the NTS. The cardiovascular response to diving is intense in aquatic animals and consists of marked bradycardia (311, 528) and peripheral vasoconstriction (127, 312), which are essential for oxygen conservation and a favorable distribution of blood flow to vital organs (310).

Marked bradycardia (77, 566, 587) and peripheral vasoconstriction (276, 517) have been reported in humans during diving or during immersion of the face in water. Vasoconstriction was noted in forearm and hand vessels, in the large arteries of the upper limb, and in capacitance vessels of the finger and forearm of humans (276, 284). Because the forearm vasoconstriction was less pronounced than the constriction of hand blood vessels, atropine was administered, but it did not augment the forearm vasoconstriction. Thus a potential role for the sympathetic cholinergic pathways to the forearm in the diving reflex was excluded (276).

UPPER AIRWAY. Electrically stimulating the central end of the superior laryngeal nerve cut close to the larynx causes apnea or hypoventilation with a slight bradycardia and a small increase in femoral vascular resistance (154). A similar response has been observed during stimulation of the nasopharyngeal receptors by retrograde infusion of a mixture of air and water from the proximal trachea. These minimal cardiovascular responses are strikingly different from those seen during the diving reflex.

Several sensory stimuli are integrated to provoke the diving reflex: 1) facial immersion activates trigeminal afferents; 2) breath holding, which facilitates vasoconstriction and bradycardia, reduces input from

the lung inflation receptors; 3) hypoxia and hypercapnia activate chemoreceptors during prolonged breath holding or diving [chemoreceptors may mediate sustained bradycardia in diving seals (149)]; and 4) as shown in ducks, cardiac vagal afferents may activate sustained bradycardia by intense peripheral vascular constriction and a blood volume shift toward the cardiopulmonary region (68).

RELATIVE CONTRIBUTIONS OF APNEA AND IMMERSION. In humans the bradycardia, hypertension, and vasoconstriction observed during the diving reflex significantly exceed those seen during breath holding alone (276) or during facial immersion while breathing air (284). The diving reflex (immersion and apnea) for a period of 30 s decreases heart rate an average of -16 beats/min and increases arterial pressure an average of +15 mmHg. The corresponding values for breath holding alone are -1 beat/min and +10 mmHg, and for immersion while breathing air the values are -4 beats/min and +1 mmHg (Fig. 2C). Although the increase in arterial pressure during immersion with apnea is only 15 mmHg, forearm and finger blood flow are markedly reduced, significantly more than during breath holding and immersion while breathing. Thus the combination of immersion and apnea causes much greater bradycardia, hypertension, and vascular resistance increase than the sum of the effects of breath holding alone and diving while breathing air.

Heistad and Wheeler (284) studied the effect of combined hypoxia and facial immersion with apnea by allowing subjects to "dive" while breathing 10% oxygen. Arterial pressure did not increase significantly, and there were reductions in heart rate, forearm blood flow, and hand flow that were not enhanced significantly over changes during the dive while breathing air. One reason the reflex lacked significant augmentation is that hyperventilation during hypoxia increased resting levels of heart rate and forearm flow and opposed in part the reflex bradycardia and vasoconstriction of facial immersion and stimulation of chemoreceptors.

The interaction could be better studied in animals. In the macaque monkey, Daly et al. (154) showed an impressive interaction between chemoreceptor stimulation and the stimulation of the upper airway receptors. Stimulating the nasopharynx and the central end of the superior laryngeal nerve causes apnea associated with minimal bradycardia and some hindlimb vasoconstriction (154), as previously observed in subprimates (34, 36, 308, 361). Moreover stimulating these afferents profoundly modified the respiratory and cardiovascular responses elicited by stimulating the carotid chemoreceptors; these stimuli suppressed the hyperventilatory response to activation of carotid chemoreceptors (153) and markedly augmented the vagally mediated bradycardia and the peripheral vasoconstriction. The latter responses were significantly greater than the sum of the separate effects of each of the two interventions.

Vestibulocerebellar Reflexes

Orthostatic reflexes consist of patterned autonomic responses to assumption of the upright posture. Although, in these adjustments, arterial baroreceptors and possibly cardiopulmonary baroreceptors with afferent vagal fibers appear important to the assumption of the upright posture, the influence of the fastigial nucleus of the cerebellum and the vestibular apparatus in the regulation of orthostatic reflexes has been investigated much less extensively. The vestibular apparatus probably feeds sensory input over the vestibular nerves to the cerebellum, the fastigial nucleus in particular, and mediates important cardiovascular changes (176). Doba and Reis (177) have shown that the fastigial nucleus is important in the cardiovascular adjustments to tilt in the anesthetized cat. After ablation of the fastigial nucleus the compensation for postural change is significantly compromised (177). Electrically stimulating the fastigial nucleus elicits cardiac acceleration and increases in arterial pressure that probably result from increases in sympathetic outflow to the peripheral circulation (176, 683). These data suggest an important contribution for vestibulocerebellar mechanisms in the cardiovascular responses to postural alterations.

INTERACTION OF SPECIFIC REFLEXES IN AUTONOMIC CONTROL OF CIRCULATION

In the intact animal or human the input from more than one group of sensory afferents frequently is changed simultaneously. Because of interactions between various reflexes, net integrated reflex responses may be difficult to predict from knowledge of responses to separate activation of each group of afferents. Furthermore reflex responses in various vascular beds differ significantly. Therefore reflex control of the circulation is the sum of integrated responses observed in several vascular beds as well as consecutive segments of the same bed during changes in input from more than one group of sensory endings.

In the following section, we present experiments that highlight five aspects of the integrated control of the circulation: 1) selectivity and nonuniformity of reflex control, 2) interaction of sensory inputs activated simultaneously, 3) redundancy of preganglionic neuron control by baroreceptors, 4) sensitization of sensory receptors and modulation of sympathetic neurotransmission, and 5) regulation of renin and vasoressin release.

Selectivity and Nonuniformity of Autonomic Control When One Sensory Afferent Input is Activated or Withdrawn

The differential responses of various vascular beds to excitatory or inhibitory reflexes have at least three major causes: 1) the differential innervation and responsiveness of various vascular segments, 2) the num-

ber and basic excitability of neuronal pools in the medulla controlling various vascular beds, and 3) the interneuronal coupling between the afferent and the efferent neuronal pools. Observations that support these are discussed below.

MECHANISMS OF SELECTIVITY. Several mechanisms that determine selectivity of responses follow.

Innervation and responsiveness of blood vessels. Most arteries and arterioles are supplied with noradrenergic vasoconstrictor fibers. The density of innervation varies from one vascular bed to another and also in consecutive vascular segments in the same vascular bed. The innervation may reach precapillary vessels and may therefore regulate not only the blood flow to each vascular bed but also the total capillary surface area available for the exchange of gases and nutrients.

Large arteries and arterioles are well innervated in the extremities and skeletal muscle, in skin, and in splanchnic and coronary beds. Adrenergic nerves in the cerebral vessels of cats and dogs could be traced to extracranial and intracranial arteries down to vessels of 15 μm in diameter but not to vessels in the brain parenchyma (201). Adrenergic nerves in the renal circulation supply the major arterial vessels in the cortex up to the afferent arteriole and the juxtaglomerular apparatus (222, 450). Recent work indicates that the tubules receive noradrenergic nerves that may regulate sodium absorption (172).

Local or tissue factors may suppress the constrictor response to the neural stimulus. These factors may be related to metabolic needs. For example, an excessive sympathetic drive to the heart increases myocardial metabolism and causes coronary arteriolar vasodilation, which overrides or suppresses sympathetic vasoconstriction.

An important phenomenon of autoregulation also occurs in several vascular beds (particularly in kidney), whereby vasodilatation opposes a reduction in flow caused by neurogenic vasoconstriction or a drop in perfusion pressure, restoring and maintaining blood flow at a constant level despite fluctuations in neurogenic tone and arterial blood pressure. Autoregulation occurs also in the cerebral and coronary circulations. Blood flow can be maintained relatively constant in these organs between arterial pressures of about 70 and 150 mmHg; the sympathetic influence on blood vessels may become apparent only outside this auto-regulatory range.

The arterioles that are most responsive to sympathetic constrictor stimuli are in the splanchnic, cutaneous, skeletal, and renovascular beds. During circulatory stress (e.g., in shock or hemorrhagic hypotension) the splanchnic, skeletal, cutaneous, and renal vasoconstrictions tend to redistribute the cardiac output away from these beds and toward the cerebral and coronary circulation, because the brain and myocardium critically depend on aerobic metabolism for their integrity.

Cutaneous and splanchnic veins as well as parenchymatous organs are well innervated; innervation of veins that drain skeletal muscle is less dense (441). Electrically stimulating splanchnic nerves at low frequency may cause a significant decrement in splanchnic blood volume, and, because ~20% of the total blood volume is in the splanchnic bed, translocating about one-half of that volume from the splanchnic circulation into the more central veins may represent a large transfusion of blood, particularly after blood loss (510). In general the venous responses are more gradual and more sustained than arterial responses. However, in humans a decrease in splanchnic blood volume may be observed during hemorrhage before splanchnic blood flow is much reduced (510). Constriction of veins and venules in the cutaneous bed may significantly regulate the rate of heat dissipation, and constriction of venules in any vascular bed determines to a large extent the levels of capillary hydrostatic pressure and capillary filtration.

The local tissue factors or autoregulatory adjustments do not seem to significantly modulate the neurogenic control of veins.

Arterial and venous dilatation may occur during withdrawal of sympathetic vasoconstrictor tone. This is passive vasodilatation. Stimulating the sympathetic cholinergic vasodilator system may cause active vasodilatation. Although the vasoconstrictor system supplies most vascular beds, the vasodilator system predominantly supplies vessels in skeletal muscle.

The density of adrenergic receptors is another major determinant of the responsiveness of a vascular bed to sympathetic stimulation or withdrawal. Arterioles contain postjunctional α -constrictor and β_2 -dilator receptors. Veins on the other hand have a predominance of α -constrictor receptors but a relative paucity of dilator β -receptors (18, 190). Extensive studies in humans indicate that intra-arterial infusion of isoproterenol, which activates β_2 -receptors, markedly dilates resistance vessels in the forearm and increases blood flow. In contrast intra-arterial isoproterenol does not change forearm venous distensibility (190). Similarly, activating α -constrictor receptors with norepinephrine or phenylephrine causes intense constriction of arterioles in skeletal muscle, in cutaneous and splanchnic beds, and in venous segments of the cutaneous or splanchnic beds. The constriction of coronary and cerebral arterioles, however, is negligible.

The density and type of prejunctional receptors (α_2 , β , dopaminergic, cholinergic, angiotensin, adenosine, etc.) modulate the release of norepinephrine from sympathetic nerves and determine the response to nerve stimulation.

Selective coupling between sensory afferents and autonomic neurons. Vasoconstriction of arterioles in muscle and paw of the forelimb of the dog are equivalent; the venoconstrictor response of veins draining the paw is much greater than that of veins draining muscle (Fig. 21). Based on these responses to electrical sympathetic nerve stimulation, one might have ex-

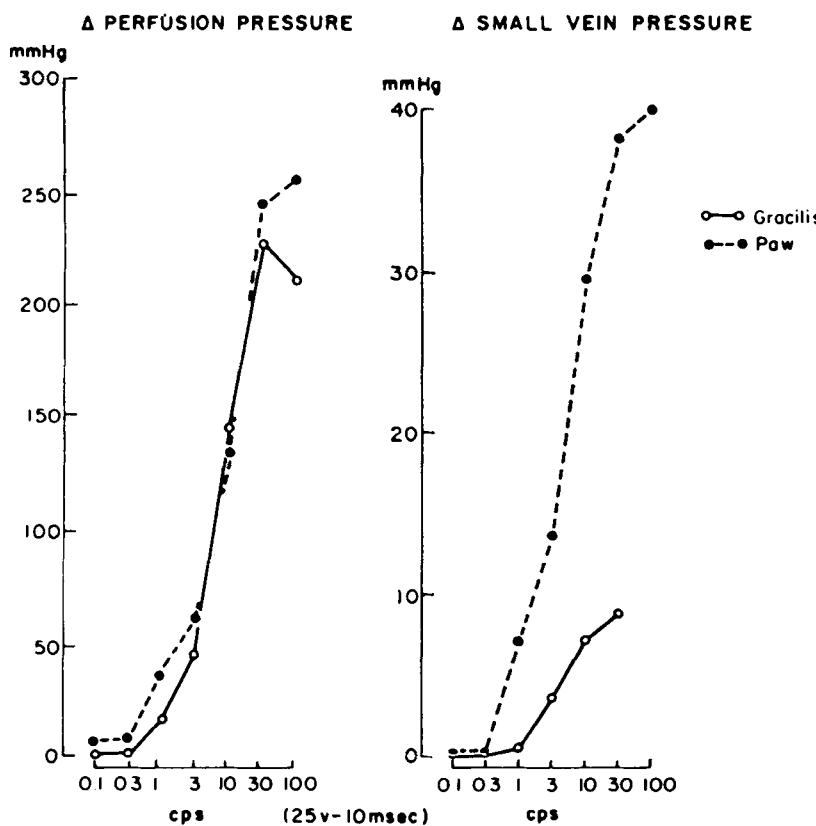


FIG. 21. Electrical lumbar nerve stimulation (0.1–100 Hz) causes significant constriction in arterioles of gracilis muscle (solid lines) and hind paw (dashed lines) of dog, as indicated by marked increases in perfusion pressures at constant blood flow. Constriction is much more pronounced in venules and veins of paw than in muscle. In contrast to responses to direct nerve stimulation, reflex vasoconstrictor responses to chemoreceptor stimulation are selective to arterioles in muscle (Figs. 16, 18). cps, Cycles per second. [From Calvelo, Abboud, et al. (96), by permission of the American Heart Association.]

pected a stimulus that uniformly excites vasoconstrictor neurons to cause constrictor responses corresponding to those seen with direct electrical stimulation of sympathetic efferents. The results obtained with the majority of excitatory reflexes indicate a marked non-uniformity of activation of sympathetic efferents. For example, chemoreceptor stimulation causes intense constriction in skeletal muscle and vasodilatation in the paw arteriole, despite adequate sympathetic constrictor innervation in both vascular beds (96). Activating sympathetic dilator fibers appears to cause the dilatation. Furthermore, despite the adequacy of sympathetic constrictor innervation to cutaneous veins, there is no venous constriction and dilatation of the larger veins has been reported (578). These experiments suggest that chemoreceptor afferents and excitatory neurons supplying arterioles or resistance vessels in muscle may be coupled and not those supplying arteriolar segments in paw or venous segments in paw and muscle.

A similar selectivity in the control of excitatory neurons to various vascular beds is seen with the baroreceptor sensory afferents. Activating baroreceptors inhibits excitatory neurons in the medulla. Conversely withdrawal of baroreceptor restraint is followed by increased sympathetic activity. Just as with activation of chemoreceptors there is nonuniformity of sympathetic excitatory outflow during withdrawal of baroreceptor restraint. Wennergren (671) indicates that withdrawal of baroreceptor restraint causes a lower rate of sympathetic discharge to the kidney than to skeletal muscle (409, 449, 671). Also a nonuniform increase in sympathetic discharge rate apparently favors resistance vessels more than the capacitance vessels in skeletal muscle (260), possibly by a ratio of 2:1. Wallin et al. (660) in 1973 recorded multiunit sympathetic activity in nerves to muscle and skin in conscious humans with a microneurographic technique and reported that, during fluctuations of arterial blood pressure, sympathetic nerve activity to muscle is much more effectively modulated by arterial baroreflexes than that to skin.

Excitability of vasomotor neuronal pool. Wennergren (671) discussed several explanations for the apparently limited arterial baroreceptor restraint on renal sympathetic excitation. One may postulate that the excitatory neuronal pool supplying the renal vasculature is limited. The finding, however, that chemoreceptor stimulation can increase renal vascular resistance significantly (501) suggests that the excitatory neurons for the renal vasculature are present in the medulla, but they may not be as effectively modulated by arterial baroreceptors as they are by the chemoreceptors.

The basic excitability of the neurons supplying renal vessels may also be less than that of neurons supplying the muscle or splanchnic beds. The mechanisms that maintain a spontaneous tonic activity of vasomotor neurons are not established. The activity appears gen-

erated largely within the medulla, because suprabulbar decerebration does not significantly change sympathetic preganglionic activity (430), whereas after acute spinal transection sympathetic activity essentially disappears acutely (479). If the medullary neurons controlling renal sympathetic activity had an unstable membrane potential reaching threshold levels for firing only intermittently as pacemaker cells do (354), they might be sensitive to their metabolic milieu and could thus function as modified chemoreceptors and fire much more frequently with changes in the chemical composition of blood than with withdrawal of baroreceptor restraint.

The chemosensitivity of these vasomotor neurons may also be mediated through chemosensitive areas located in the brain stem. Electrically stimulating two such areas on the ventral surface of the medulla increases blood pressure and ventilation (405, 465). Another area in the lateral medulla triggers marked pressor responses and increased sympathetic activity when exposed to cerebrospinal fluid at a low pH (644).

A study of Pelletier and Shepherd (501) supports the concept of an inherently lower discharge rate in renal vasomotor neurons, which can be sensitized by chemical stimuli. They studied responses of muscle, skin, and renal vessels to bilateral carotid occlusion during control conditions and during hypoxia, which excites vasomotor neurons. Hypoxia significantly augmented the increase in renal sympathetic nerve activity and renal vasoconstrictor responses during carotid occlusion, whereas the constrictor responses of muscle vessels were only slightly increased during carotid occlusion. Thus the increased excitability of neurons that are under the restraining influence of baroreceptors results in a much higher rate of firing as soon as the baroreceptor restraint is removed.

A third possibility is that the renal excitatory neurons, in contrast to the muscle neurons, are more restrained by cardiopulmonary baroreceptors than by the arterial baroreceptors. When the ventricular receptors or their afferent fibers are stimulated, the vasodilator response is greater in renal than in skeletal muscle vessels (403, 482, 483). In contrast the arterial baroreceptors inhibit the renal and skeletal muscle beds to a similar extent. Furthermore the maximal dilatation attained in skeletal muscle with intense cardiac afferent stimulation is less than that attained with baroreceptor stimulation. These findings suggest that the renal vasomotor neurons are more effectively coupled with ventricular receptor afferents than the skeletal muscle neurons and that the latter are more effectively coupled with arterial baroreceptor afferents. This pattern of central organization would satisfy the requirements for a desirable circulatory adjustment. Changes in skeletal muscle vascular resistance would buffer large changes in arterial blood pressure, whereas changes in blood volume, which are sensed predominantly by cardiopulmonary afferents, would be buffered by changes in renal sympathetic activity,

which would in turn have a much greater role in regulating body fluid volume and sodium balance.

Threshold, hysteresis, and resetting of baroreceptor afferents. The baroreceptors may have different thresholds of activation; fibers with higher thresholds might be coupled centrally with, for example, cardiac vagal neurons, whereas fibers with lower thresholds might be coupled with sympathetic preganglionic neurons to skeletal muscle or to kidney. The reflex bradycardia caused by an increase in carotid sinus pressure begins at a higher level of arterial pressure (higher threshold) than the reflex vasodilatation in skeletal muscle or kidney. This differential effect may be accounted for by the relative number of medullated versus nonmedullated afferents projecting to the various preganglionic neurons.

The baroreflex response may also have a significant degree of hysteresis. The magnitude of the response obtained (e.g., at a given intrasinus pressure) depends on whether this pressure level is reached by elevating the pressure from a lower level or by lowering the pressure from a higher level (85). When the blood pressure is reached by lowering the pressure, the carotid sinus fires less for the same carotid distending pressure. Also, when arterial pressure is elevated for even a few minutes, the sensitivity of the reflex is reduced and its threshold is increased (119). This is referred to as resetting the baroreceptors, and mechanical or electrical events could cause the phenomenon [e.g., stress relaxation, a change in distensibility, or an augmentation of postexcitatory depression (85)]. More work is necessary before the mechanism is clarified.

EXAMPLES OF SELECTIVITY AND NONUNIFORMITY. *Simultaneously activating sympathetic and parasympathetic efferents.* For too long the prevailing view has been that reflex activation of sympathetic efferents is associated only with simultaneous withdrawal of parasympathetic efferents. However, simultaneous activation of sympathetic and parasympathetic efferents does sometimes occur. For example, the diving reflex and the chemoreceptor reflex activate parasympathetic efferents to the heart and sympathetic efferents to the peripheral circulation, causing intense vasoconstriction (274, 280, 282).

Marked bradycardia is seen during diving and during stimulation of chemoreceptors, particularly if hyperventilation is prevented. Peripheral vasoconstriction favors oxygen delivery to the coronary circulation. When this is coupled with a reduced myocardial oxygen demand as a result of bradycardia and activated parasympathetic cholinergic vasodilator fibers to the coronary circulation, the protective effect of the reflex is optimal.

Simultaneously inhibiting parasympathetic and sympathetic efferents. The slowly adapting pulmonary stretch receptors cause reflex tachycardia and vasodilatation by inhibiting the cardiac vagal neurons and

reducing sympathetic vasoconstrictor outflow to skeletal muscle. This promotes an increase in cardiac output and diverts blood flow to skeletal muscle during hyperventilation. Emotional stress or the defense reaction may be accompanied by parasympathetic withdrawal through an inhibition of cardiac vagal neurons, and vasodilatation in skeletal muscle partly through sympathetic withdrawal and inhibition of constrictor neurons (301). The combined stimulation of arterial baroreceptors and of the posterior hypothalamus results in tachycardia through parasympathetic withdrawal and in vasodilatation through sympathetic withdrawal [Fig. 22; (375)].

Selective and differential influence of two major inhibitory afferents: arterial and cardiopulmonary. Afferent impulses originating in arterial and cardiopulmonary baroreceptors during hypertension and hypervolemia inhibit sympathetic and activate vagal neurons. Conversely hypotension and hypovolemia unload these receptors and reflexly increase sympathetic activity and decrease vagal efferent activity. Although the afferent nerves from these receptor regions project to the NTS, the physiological responses to their activation or unloading are not identical, suggesting that they do not converge on the same neurons in the medulla. The preceding paragraphs refer to differential control of renal versus muscle resistance vessels by these two sets of inhibitory afferents. A selectivity of responses has been demonstrated with these two inhibitory reflexes in humans.

Activating afferents. During electrical stimulation of the carotid sinus nerve in humans, reflex bradycardia and hypotension are demonstrated but there is no evidence of venodilatation (199). This selective control of efferent autonomic pathways can be seen during activation of carotid sinus mechanoreceptors by applying negative pressure with a neck suction box in humans to simulate hypertension (186). Reflex bradycardia and hypotension occur without a significant increase in forearm blood flow or forearm vasodilatation. In contrast a significant increase in forearm flow is demonstrated readily during elevation of the legs, a maneuver that increases central venous pressure and activates cardiac mechanoreceptors (15, 535).

Inhibiting or unloading afferents. Selective unloading of cardiopulmonary and not arterial baroreceptors may be accomplished in humans by applying negative pressure to the lower half of the body with a suction box. This is described in the chapter by Mark and Mancia in this *Handbook* in greater detail. Minimal lower-body negative pressure (LBNP) decreases cardiac filling pressure without changing systemic arterial pressure (689). This triggers reflex vasoconstriction in forearm vessels and minimal splanchnic vasoconstriction but does not change heart rate (7, 326, 669). Conversely, selective unloading of carotid baroreceptors with neck compression causes tachycardia, a rise in arterial pressure, and a small increase in forearm vascular resistance (435).

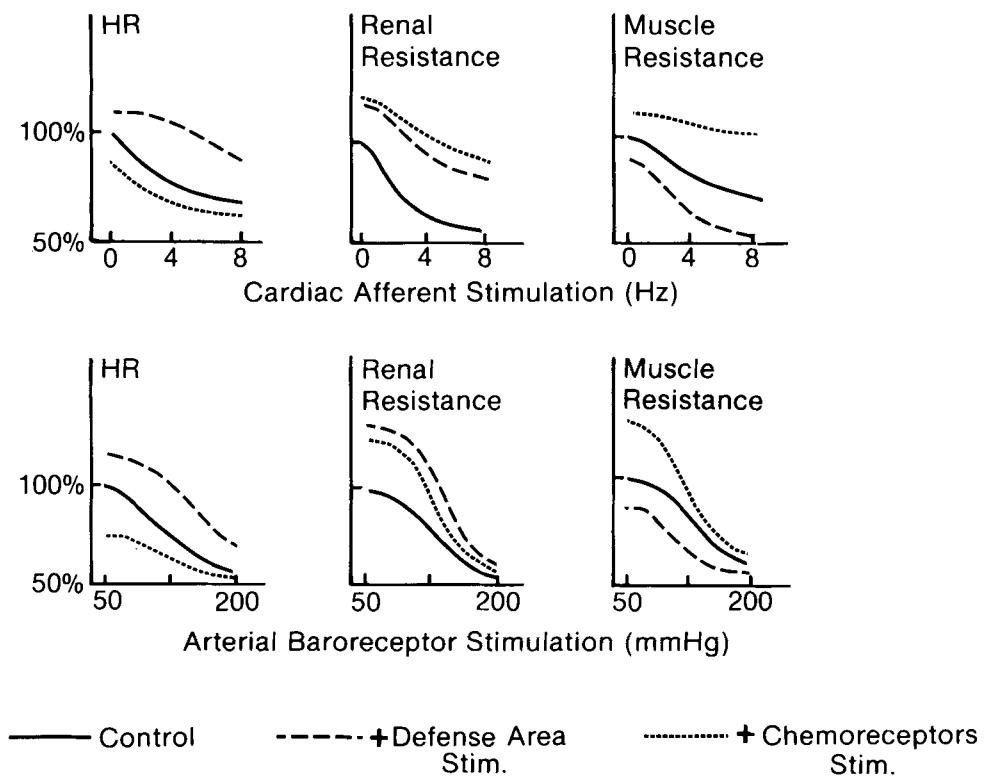


FIG. 22. Changes in heart rate (HR) and renal and muscle resistances during stimulation of cardiac afferents (upper panels) and arterial baroreceptors (lower panels). Both sets of afferents are inhibitory with some selectivity. For example, cardiac afferents cause a significantly greater inhibition of renal resistance. Interactions between arterial baroreceptors and cardiac afferents and input from chemoreceptors and hypothalamic defense area cause a variety of responses. Variable interactions point to specificity in patterns of afferent convergence on various groups of brain stem neurons or connecting pathways. For example, chemoreceptor stimulation prevents cardiac afferents from inhibiting skeletal muscle resistance but does not influence inhibitory influence of arterial baroreceptors. (Schematic drawn from data in refs. 5, 12, 278, 365, 375, 671–673).

When LBNP increases to levels of -40 or -60 mmHg, excessive pooling lowers arterial pressure, withdrawing tonic arterial and cardiopulmonary baroreflex restraint. This results in tachycardia, a significant increase in splanchnic vascular resistance, and a slightly greater increase in forearm resistance than was seen with minimal levels of LBNP. There is little or no evidence of reflex venoconstriction (Figs. 23, 24). Although venous tone does not increase reflexly in the extremities of humans during either marked LBNP or upright tilt (15), splanchnic venous tone increases during hemorrhage in humans (510).

These results and those observed during neck suction suggest that in humans the arterial baroreflexes significantly regulate heart rate and splanchnic resistance but forearm vessels to a lesser degree, whereas cardiopulmonary reflexes predominantly regulate the resistance vessels in the forearm. With no information on the relative influence of these two receptor regions on the renal circulation in humans, a differential effect similar to that seen in animals cannot be excluded in humans.

Activating carotid baroreceptors when sympathetic tone is elevated. The evidence for the limited capacity of carotid baroreceptors to regulate vascular resistance

in the forearm of humans was tested further because of the possibility that forearm vessels may not dilate during neck suction when sympathetic tone is very low. However, even when excessive LBNP increases sympathetic tone so that forearm and splanchnic resistances are high and heart rate is increased, activating carotid baroreceptors with neck suction suppresses only the reflex tachycardia and splanchnic constriction, not the vasoconstriction in the forearm (7). The carotid baroreceptors in humans selectively inhibit the excitatory sympathetic pathway to splanchnic vessels and the heart but not to the forearm vessels. This apparently provides the human corollary to the findings of Gebber et al. (237), who carried out electrophysiological studies on the organization of central vasopressor pathways. Their results indicate that activating baroreceptor afferents blocks certain vasoconstrictor pathways without interfering with others. Their findings emphasize the selectivity of central synaptic connections between various pathways.

Simultaneously Activating Sensory Stimuli

Two general kinds of interactions may take place.
1) Two groups of sensory afferents that cause opposite

responses may be activated simultaneously. Whether the net effect is zero or whether the effect of one sensory afferent overrides the other is an important consideration. 2) The tonic input of one set of sensory afferents may modulate the response to another set of afferents.

STIMULATING TWO OPPOSING REFLEXES. Following are three examples of conditions in which opposite responses are triggered simultaneously. Cardiac sensory afferents that inhibit sympathetic drive are stimulated 1) by inflating a balloon in the ascending aorta, causing acute left ventricular distension (435); 2) by occluding the circumflex coronary artery, causing ischemia of the posterior wall of the ventricle (620); or 3) by coronary arteriography (189). Arterial hypotension simultaneously reduces the activity of arterial baroreceptors and increases sympathetic drive. The net response is inhibition of sympathetic outflow and bradycardia (189, 434, 616, 620). Thus the cardiac reflex overrides the effects of arterial hypotension.

The syncope associated with aortic stenosis or with vasovagal syncope may represent overactivated cardiac afferents inhibiting sympathetic activity despite reductions in arterial pressure (436, 637).

MODIFYING REFLEX GAIN BY CHANGING TONIC INFLUENCE OF ONE SET OF SENSORY AFFERENTS. The tonic input from one set of sensory receptors may alter the reflex response to stimulation of another group of sensory afferents. For example, increases or decreases in arterial baroreceptor input may modify the response

to chemoreceptor stimulation or the tonic input from the cardiac vagal afferents may modify the effects of changes in the activity of arterial baroreceptors or chemoreceptors on blood pressure, renin release, antidiuretic hormone (ADH) release, and other variables. A significant degree of selectivity may exist in these interactions and may have physiological implications dependent on the nature of the central projections of the afferents and their neuronal connections. There are also important pathophysiological states where the input from arterial and cardiac receptors may be suppressed, as in hypertension or heart failure. Under those conditions, responses to activation of somatic afferents during exercise or activation of chemoreceptors with hypoxia might be drastically modified. Several important interactions can illustrate these concepts.

How carotid baroreceptors modulate the chemoreceptor and somatic reflexes. At low carotid sinus pressure the gains of the chemoreceptor and somatic reflexes are augmented, but at high pressure the reflexes are suppressed (Fig. 22).

Carotid baro- and chemoreceptors. Elevating carotid sinus pressure in the left carotid artery of the dog suppresses the vasoconstrictor response to stimulation of the chemoreceptor reflex. Perfusioning the right carotid artery with hypoxic, hypercapnic blood at constant perfusion pressure activates the chemoreceptor reflex. Conversely a reduction in arterial pressure induced by hemorrhage augments the vasoconstrictor response to chemoreceptor stimulation (278).

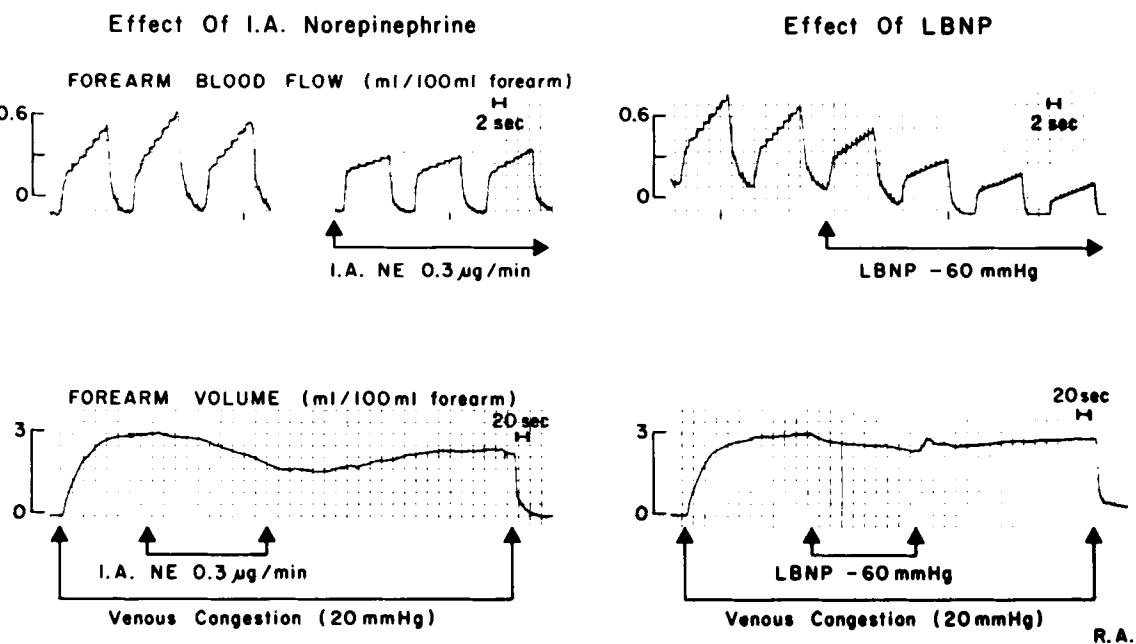


FIG. 23. Reduced forearm blood flow (plethysmographic tracings in *upper panels*) and forearm volume at constant venous congesting pressure of 20 mmHg (*lower panels*) indicate increases in arteriolar resistances and venous tone, respectively. Responses are to intra-arterial infusions of norepinephrine (*left panels*) and to lower-body negative pressure (*right panels*) sufficient to lower arterial pressure and pulse pressure (*right panels*). Arteriolar constriction was comparable with 2 interventions, but venous tone increase was negligible during LBNP compared to intra-arterial NE. [From Abboud et al. (12).]

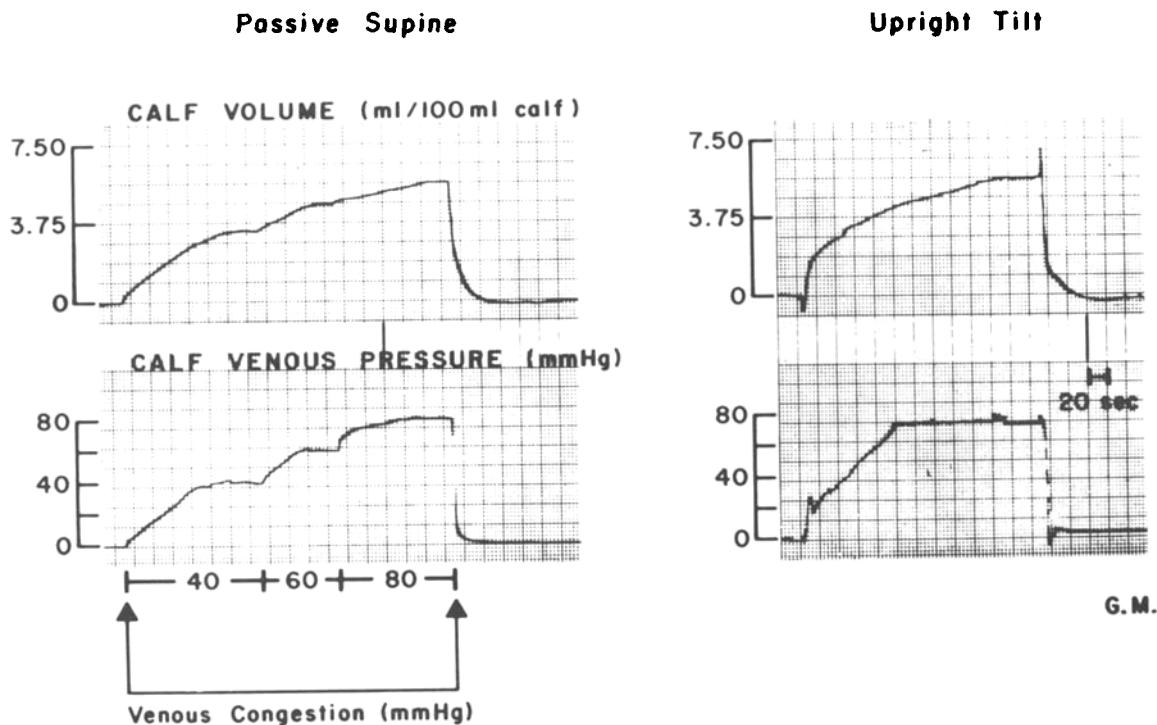


FIG. 24. Upright tilt does not increase venous tone in calf of humans. Veins of limbs are not sensitive to arterial or cardiopulmonary baroreflexes, but arterioles are. Other venous segments, e.g., splanchnic veins, are sensitive to these baroreflexes, whereas veins of extremities are more sensitive to temperature or respiratory reflexes (cf. Fig. 23). [From Abboud et al. (12, 15).]

A similar interaction occurs with the hyperventilatory response to chemoreceptor stimulation, which is augmented at low carotid sinus pressure [Fig. 25; (279)].

Somatic receptors and baroreceptors. Activating somatic afferents by contracting skeletal muscle or electrically stimulating the central end of the cut sciatic nerve at high frequency causes reflex vasoconstriction in the isolated perfused gracilis muscle, renal vasoconstriction, increases in arterial pressure, and tachycardia. The reflex vascular responses are augmented significantly when the carotid sinuses are perfused at low pressure and inhibited when the carotid sinuses are perfused at high pressure (437, 615). A change in vascular reactivity to the released neurotransmitter, norepinephrine, does not cause this interaction in the gracilis muscle.

These two sets of experiments show that the inhibitory influence of arterial baroreceptors on excitatory neurons is predominant and sufficient to block the excitatory responses to the chemoreceptors or the somatic reflex. Clinical implications of these interactions in hypertensive states are discussed in the next section.

How cardiopulmonary vagal afferents modulate other reflexes. The cardiopulmonary vagal afferents modulate changes in vascular resistance, ADH release, and renin release mediated by chemoreceptor, somatic, and arterial baroreceptor reflexes.

Cardiopulmonary and arterial baroreceptors. Carotid hypotension increases arterial pressure and vas-

cular resistance in the gracilis muscle in dogs with cut aortic depressor nerves. Bilateral vagotomy in these animals augments this carotid baroreflex (356). The tonic inhibitory input from the cardiopulmonary vagal afferents apparently reduces the gain of the arterial baroreceptor reflex control of vascular resistance, particularly in the lower range of arterial blood pressure. Thus, during hemorrhage when cardiac filling pressure and arterial pressure drop, the two reflexes synergistically interact to significantly increase vascular resistance. Conversely, increasing the activity of cardiac sensory afferents as, for example, in myocardial ischemia, decreases the gain of the carotid baroreflex (656).

The altered gain of the arterial baroreflex by the increase or decrease in the input from cardiac vagal afferents indicates that the combined effect of the two sensory inputs is more than a simple algebraic summation of individual responses and represents an interaction between the two reflexes. This interaction was explored in humans by applying LBNP or elevating the legs to modify the cardiopulmonary input. The reflex bradycardia during neck suction or phenylephrine-induced hypertension was not modified (605). Possibly the interaction is evident only during carotid hypotension and for changes in resistance rather than heart rate.

Chemo- and cardiopulmonary receptors. The response to chemoreceptor stimulation is augmented when the cardiopulmonary vagal afferents are absent (356). The reflex vasoconstrictor response to nicotine

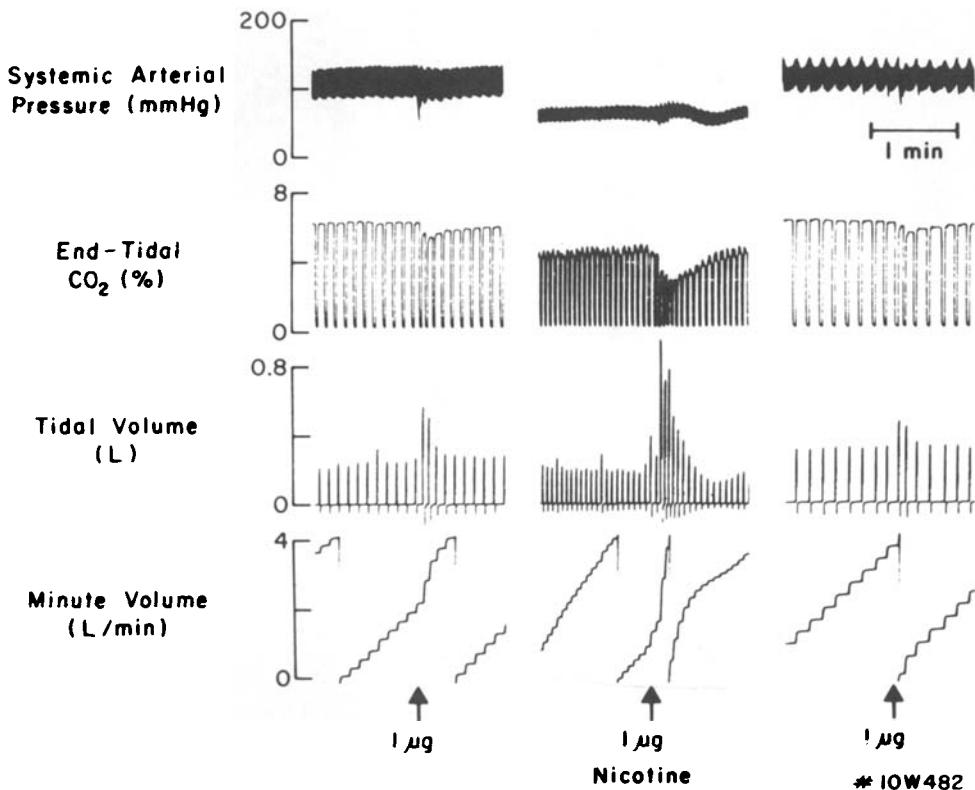


FIG. 25. Hyperventilatory response to stimulating carotid chemoreceptors with nicotine is augmented during systemic hypotension and inhibited during hypertension in anesthetized dogs. The rise in systemic arterial pressure suppresses base-line ventilation, which tends to increase during hypotension. [From Heistad, Abboud, et al. (279).]

or cyanide injection into the carotid arteries was significantly greater after vagotomy than before vagotomy in animals in which aortic depressor nerves had been cut and carotid sinus pressure was maintained constant.

Wennergren et al. (673) also examined the interaction between cardiac afferents and the chemoreceptors by stimulating both sensory inputs. The right inferior cardiac nerve, which runs from the heart to the main vagal trunk, was cut, its central end stimulated electrically and the chemoreceptors activated by perfusing the carotid arteries with venous blood. Stimulating the cardiac afferents reduces the vasoconstrictor response to the chemoreceptor stimulus only slightly in muscle and kidney. This is in contrast to the significant inhibition of the chemoreceptor reflex that is seen when the arterial baroreceptors are stimulated (278).

The physiological significance of this interaction is that during the diving reflex the chemoreceptor activation by hypoxia causes peripheral vasoconstriction, which is beneficial for oxygen conservation; the central blood volume increase that may occur under these circumstances would not reverse that beneficial peripheral vasoconstriction. It would on the other hand enhance the reflex bradycardia (68).

Cardiopulmonary and somatic afferents. Electrically stimulating the central end of the cut sciatic

nerve in anesthetized sinoaortic denervated dogs activates somatic afferents; arterial pressure and heart rate increase and renal blood flow decreases. During hypervolemia caused by intravenous infusion of dextran the renal vasoconstrictor reflex is reduced, whereas immediately after vagotomy it is augmented [Fig. 26; (615)]. The interaction is less evident with the increases in arterial pressure and heart rate.

A similar interaction occurs in humans during stimulation of somatic afferents. In normal subjects, performing isometric exercise of the left arm by compressing a dynamometer with a handgrip for 1–2 min activates somatic afferents; reflex responses include a rise in arterial pressure, an increase in heart rate, and an increase in resistance of the resting forearm. This reflex response is augmented when the input from the cardiopulmonary afferents is reduced by LBNP (657).

Thus in animals and humans cardiopulmonary vagal afferents may modulate the magnitude of the reflex response during exercise. This interaction may explain the differences in responses to exercise in the supine position in contrast to the upright position. It is tempting to speculate that an augmented noradrenergic response to exercise in heart failure, documented in patients, is related to the decreased input from cardiac vagal afferents as the result of damage to these endings in heart failure.

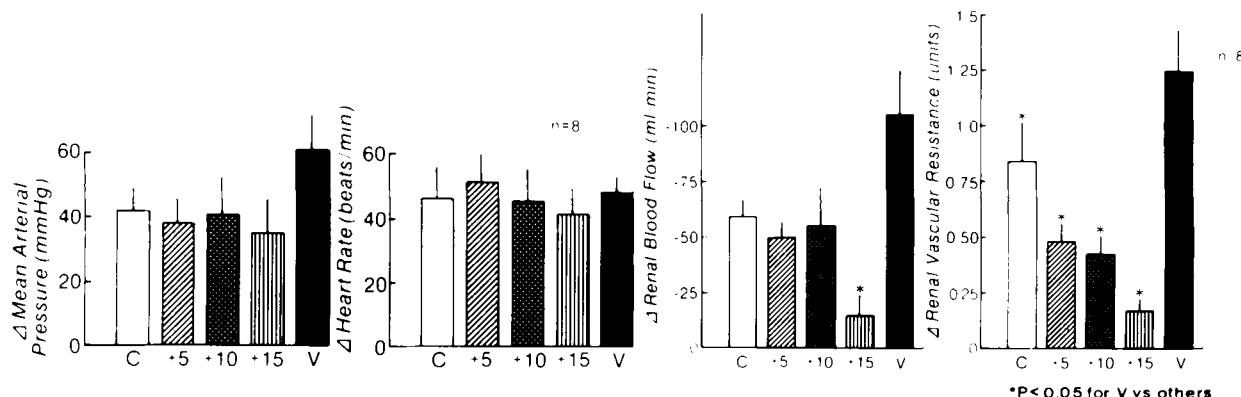


FIG. 26. Responses (means \pm SE) to electrical stimulation of somatic afferents during volume expansion and after bilateral vagotomy (V). Volume expansion with +5, +10, and +15 ml/kg of 6% dextran in normal saline suppressed reflex renal vasoconstrictor response to electrical stimulation of somatic afferents in dogs with sinoaortic deafferentation as compared to control (C). Bilateral vagotomy markedly increased reflex vasoconstriction. Neither volume expansion nor vagotomy altered reflex increases in arterial pressure or heart rate. [From Thames and Abboud (615).]

Stimuli that may alter arterial or cardiopulmonary reflexes. Just as the tonic influence of arterial and cardiopulmonary receptors on other reflexes is significant, several stimuli may conversely alter the baroreflexes significantly. Exercise and arterial baroreceptor gain. Experiments in animals and humans indicate that during exercise the baroreflex control of arterial pressure is unchanged and that the tachycardia does not result from insensitivity of arterial baroreceptors [(57, 415, 421); see also BARORECEPTOR REFLEX DURING EXERCISE, p. 706.]

Interaction of thermoreceptors and baroreceptors in control of cutaneous blood flow. Thermoreceptors mediate responses that modify vascular tone in cutaneous beds to increase or decrease heat dissipation. In addition thermal reflexes may modify other reflex responses. Several investigators have reported that central-body heating and local heating attenuate reflex constrictor responses in cutaneous veins (20, 541, 657, 667, 688). Also heating a portion of the body without changing central-body temperature may attenuate constrictor responses of cutaneous veins to exercise (541) and responses to deep breath or mental arithmetic (688). Crossley et al. (139) reported that reflex vasoconstriction of forearm resistance vessels with LBNP persists during total-body heating. We have found that heating one forearm in humans interferes with reflex vasoconstrictor response in the cutaneous bed of the opposite arm. Immersing one forearm in warm water (35°C - 37°C) markedly inhibits the reflex vasoconstrictor response to LBNP in the contralateral finger but alters the response of the contralateral forearm only slightly. Reducing the temperature of the water to 10°C - 12°C increases the reflex vasoconstrictor response to LBNP. Thus the baroreceptor reflex effect on blood flow to the fingers is inhibited when the input from thermoreceptors signals an increase in skin temperature. This interaction does not extend as effectively to vessels of the forearm, presum-

ably because the forearm is predominantly a skeletal muscle bed rather than a cutaneous bed (139, 277). Thus an inhibitory input overrides the excitatory reflex from arterial and cardiopulmonary baroreceptors in the control of blood flow to the fingers and possibly to the cutaneous circulation in general. This subserves a beneficial function because the major role of the cutaneous circulation is to dissipate or retain heat rather than to contribute to the buffering of changes in arterial blood pressure or changes in blood volume.

Interaction between stimuli of defense area and cardiac or arterial baroreceptor afferents. As discussed in *Hypothalamus and Cardiovascular Control*, p. 686, stimulating the defense area causes tachycardia and vasoconstriction in different vascular beds, including the renal and splanchnic beds, but it causes vasodilation in skeletal muscle. Wennergren et al. (672) studied the interaction between stimulation of the defense area and simultaneous activation of the cardiac afferents by electrical stimulation of cardiac afferent nerves (Fig. 22). Stimulating cardiac afferents causes reflex bradycardia and gastric relaxation by activating vagal efferents and reflex vasodilatation by withdrawing sympathetic tone to various vascular beds, particularly the renal circulation. Simultaneously stimulating the defense area opposes and reverses the effects of stimulating cardiac afferents on heart rate and gastric relaxation. On the other hand the inhibitory effects of cardiac afferents on the renal circulation were apparent though from a higher baseline resistance because of the sympathetic drive from the defense area, and the skeletal muscle vasodilatation was enhanced because both stimuli were synergistic in producing a greater muscle vasodilatation (Fig. 22).

Interaction between carotid bodies, upper airway receptors, and apnea in cardiac arrest. Daly et al. (150) have an excellent review on the clinical implications of these interactions.

If the chemoreceptor stimulus is associated with apnea or, as often seen during the diving reflex, with stimulation of receptors in the larynx or nasopharynx innervated by the trigeminal nerve, then the bradycardia and systemic vasoconstriction can be intense. This interaction could certainly lead to cardiac arrest and sudden death. Some premature and full-term infants have bouts of periodic breathing and apneic spells in the expiratory phase lasting up to 30 s or more. Bradycardia, hypoxia, cyanosis, and hypotonia occur during the apneic spells. The bradycardia is vagally mediated. It could result from excitation of the peripheral arterial chemoreceptors active in premature (531) and full-term (138) infants and infants with periodic breathing (531). If the upper airways are also obstructed, which causes a diminution or cessation of respiratory effort in some infants (137, 462), particularly those who are periodic breathers, then prolonged cardiac arrest could result in sudden death.

The reflex bradycardia induced by stimulation of arterial baroreceptors, like the bradycardia evoked by chemoreceptor stimulation, is more predominant during expiration than inspiration. Several investigators have described this interaction and analyzed the electrophysiological mechanisms involved. Eckberg, Abboud, et al. (185, 186, 188, 189) and Trzebski et al. (643) have demonstrated clearly that in humans carotid suction during inspiration has very limited influence on the R-R interval, whereas the response during expiration is pronounced. Thus, during asphyxia caused by stimulation of the upper airway reflexes, the combination of hypoxia, apnea, vasoconstriction, and possibly hypertension all converge to induce a marked activation of vagal neurons, severe bradycardia, and possibly cardiac arrest.

Redundancy in Baroreceptor Control of Preganglionic Neurons

Three major groups of cardiovascular sensory afferents can be activated mechanically: carotid baroreceptors, aortic baroreceptors, and cardiopulmonary baroreceptors. Their mechanical activation induces reflex slowing of the heart predominantly through stimulation of vagal efferents and reflex vasodilatation through inhibition of sympathetic efferents. These afferents not only play a major role in the acute circulatory adjustments to cardiovascular stresses, but they may be important in the more chronic modulation of sympathetic drive, vascular tone in hypertensive states, and heart failure.

Most investigators use the reflex changes in heart rate in response to acute changes in arterial blood pressure as an index of the sensitivity and integrity of the baroreceptor reflex in intact animals or humans (425, 516, 586, 640). Infusions of phenylephrine raise pressure, and infusions of nitroglycerin lower arterial pressure.

There are several important questions in relation to integration of input from the baroreceptors. For ex-

ample, does the baroreflex control of heart rate represent the baroreflex control of resistance or sympathetic efferent activity; is there a redundancy in the control of heart rate or vascular resistance by the various afferents; what do cardiopulmonary afferents or other afferents contribute to the reflex response to phenylephrine or nitroglycerin, and conversely, what do sinoaortic baroreceptors contribute to the reflex response to volume expansion and activation of cardiopulmonary vagal afferents? Numerous investigators (35, 347, 427, 548, 654) have tried to answer some of these questions. To clarify these issues the next section reviews a series of systematic studies in anesthetized rabbits (255).

Studies in anesthetized rabbits with the hindlimb perfused with a pump at constant blood flow allowed reflex changes in hindlimb vascular resistance to be compared to changes in heart rate during intravenous infusions of phenylephrine and nitroglycerin. By interposing a delay coil between the pump and the hindlimb, reflex changes in hindlimb resistance were detected before the drugs reached the area. With sequential, random denervation of the carotid, aortic, and vagal afferents, the restraining influence of each set of afferents on the circulation and their relative contribution to reflex responses to phenylephrine-induced increases and nitroglycerin-induced decreases in arterial pressure could be assessed.

RESTRAINT OF RESTING ARTERIAL PRESSURE, VASCULAR RESISTANCE, AND HEART RATE BY VARIOUS AFFERENTS. Bilateral carotid or aortic baroreceptor denervation significantly and abruptly increases arterial pressure, perfusion pressure, and heart rate, which tend to decline gradually toward control values. The responses to either aortic or carotid baroreceptor denervation are comparable in this preparation and support results obtained in awake rabbits by Chalmers et al. (102). Increases in vascular resistance and arterial pressure were on the average twice as large, however, when the second or remaining set of arterial baroreceptors was sectioned than when only one set was cut and the other remained intact [Fig. 27; (25)]. Thus the aortic and carotid baroreceptor afferents may exert similar degrees of restraint on the autonomic neurons, but the degree of restraint of either one nearly doubles with respect to perfusion pressure and arterial pressure in the absence of the other set.

Bilateral vagotomy with intact aortic and carotid baroreceptor afferents causes only small increases in arterial pressure and perfusion pressure. After sinoaortic denervation, however, bilateral vagotomy causes a much greater rise in arterial pressure and perfusion pressure (Fig. 27). These results suggest that the restraining influence of a remaining set of baroreceptor afferents increases significantly and may often be sufficient to prevent significant increases in pressure and resistance. After the abrupt increases in vascular resistance and arterial pressure with sequential denervation of the three groups of afferents, vascular resis-

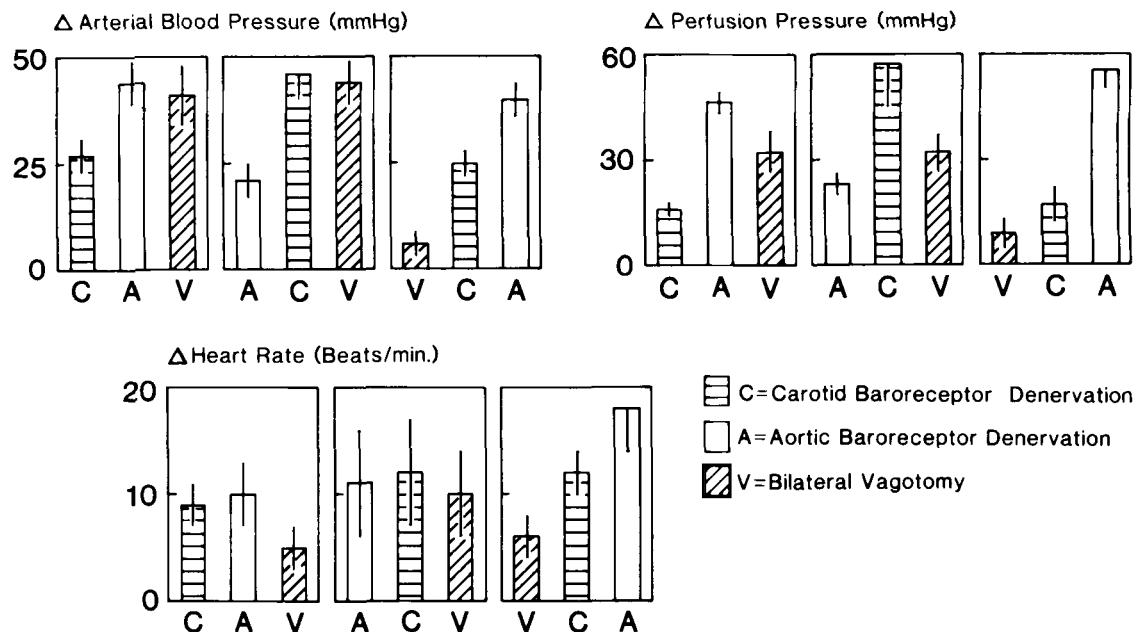


FIG. 27. Effect of sequential denervation of carotid sinus nerves (C), aortic afferents (A), and vagi (V) in anesthetized rabbits. Means \pm SE of increases in arterial pressure, perfusion pressure in the hindlimb (perfused at constant blood flow), and heart rate are shown. Denervation of carotid sinus nerves when aortic afferents are intact or after vagotomy causes much smaller increases in arterial pressure and perfusion pressure than their denervation after aortic afferents are cut. The same is true for aortic nerves before and after section of carotid sinus nerves and vagotomy. Also bilateral vagotomy causes much smaller increases in pressures when carotid and aortic afferents are intact than when they have been cut. These interactions are not apparent with respect to heart rate.

tance seems to level off at a level lower than that immediately after denervation. This suggests some additional readjustment of the sympathetic excitatory activity to a lower level independent of baroreceptors or a change in the responsiveness of vascular muscle to sympathetic drive (255).

REFLEX RESPONSES TO PHENYLEPHRINE AND NITROGLYCERIN AFTER SELECTIVELY DENERVATING BARORECEPTORS. Major differences in the baroreflex control of heart rate and of vascular resistance in the hindlimb are apparent after partial baroreceptor denervation.

Partial baroreceptor denervation. Section of either the aortic or the carotid baroreceptors significantly impairs the control of heart rate during changes in arterial blood pressure without interfering with the reflex control of hindlimb resistance. This differential influence must be due to the fact that heart rate responses are modulated predominantly by efferent vagal neurons, particularly during phenylephrine infusions, whereas vascular responses are regulated predominantly by efferent sympathetic neurons (255).

Numerous investigators have addressed the degree to which one set of arterial baroreceptor afferents may compensate for the absence of the other. Responses to combined stimulation of both sets of baroreceptors is much less than the sum of the individual responses (255). In *Mutual inhibition or redundancy in sympathetic neuron control*, p. 678, this is discussed and referred to as evidence for a mutual inhibitory addition of the various sets of sensory afferents (Fig. 2). We refer to this concept in terms of redundancy of autonomic neuron control by the baroreceptor afferents. The results obtained in anesthetized rabbits indicate no redundancy of vagal neuron activation by baroreceptors but nearly total redundancy of inhibition of sympathetic neurons to the hindlimb (Fig. 28). These differences may be related to the pattern of convergence of impulses from aortic and carotid baroreceptor afferents on vagal and sympathetic preganglionic neurons or on central pathways for these reflexes.

Contribution of cardiopulmonary baroreceptors and other mechanoreceptors to reflex responses to phenylephrine and nitroglycerin. After sinoaortic denervation reflex bradycardia and vasodilatation are still observed during marked increases in arterial pressure with phenylephrine, but there is no significant response to nitroglycerin-induced hypotension. Bilateral vagotomy abolishes these residual responses, which suggests that they are mediated through vagal afferents. Activating mechanoreceptors in the cardiopulmonary region during phenylephrine infusion may trigger these inhibitory reflexes after sinoaortic denervation. Whether cardiopulmonary baroreceptors normally contribute to the reflex responses to phenylephrine- and nitroglycerin-induced changes in arterial pressure when sinoaortic baroreceptors are intact is

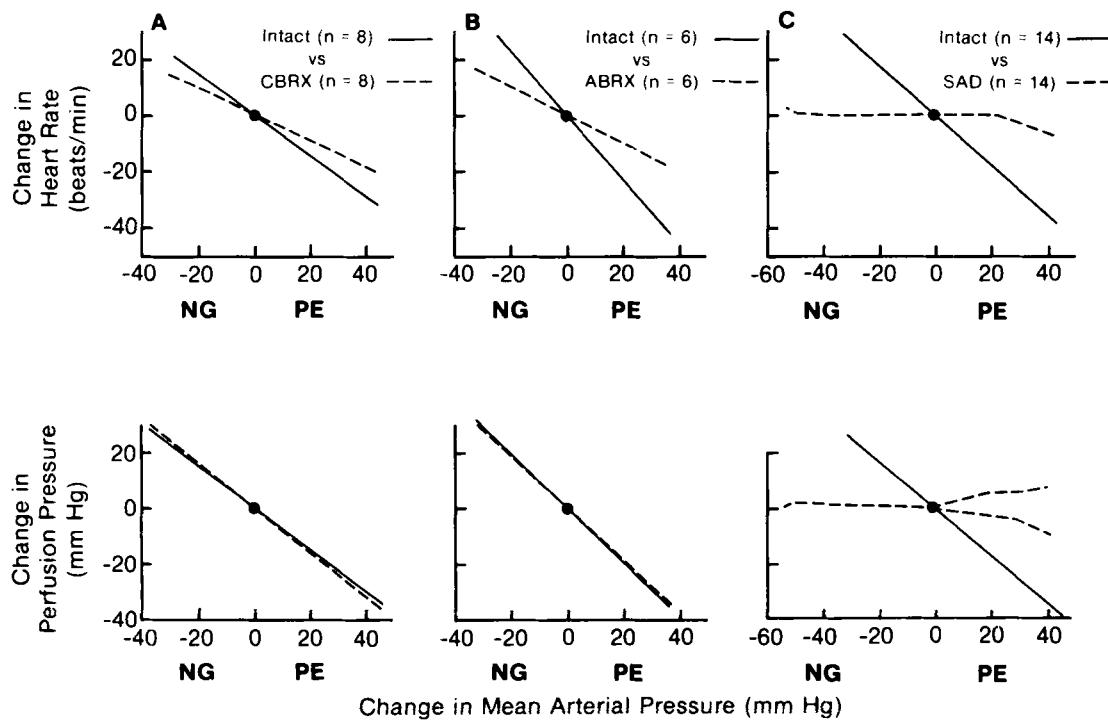


FIG. 28. Reflex changes in heart rate (*upper panels*) and in hindlimb perfusion pressure (*lower panels*) in anesthetized rabbits during changes in arterial pressure provoked with phenylephrine (PE) and nitroglycerin (NG). Solid lines, control responses; dashed lines, responses after section of carotid sinus nerves (CBRX; *A* panels) or aortic nerves (ABRX; *B* panels), or after sinoaortic denervation (SAD; *C* panels). Sectioning 1 set of afferents significantly reduces gain of baroreflex control of heart rate but not of hindlimb vascular resistance. [From Guo, Thames, and Abboud (255), by permission of the American Heart Association.]

unknown. If they do then these interventions may not be used with confidence to assess the status of arterial baroreceptors. Results of our experiments in anesthetized rabbits indicate that vagal afferents do not significantly contribute to the reflex control of hindlimb resistance vessels. The participation of these vagal afferents is significant, however, after sinoaortic denervation (Fig. 28) and should be considered when evaluating the baroreflex control of the circulation during arterial pressure increases in pathological states where arterial baroreflexes may be impaired (e.g., hypertension) (19, 289, 582).

Sympathetic afferents may also contribute to the reflex response to phenylephrine-induced hypertension, but, like the vagal afferents, their contribution is negligible when the sinoaortic baroreceptors are intact (86, 206, 419).

Clearly, however, using reflex changes in heart rate with phenylephrine and nitroglycerin to indicate the overall arterial baroreceptor reflex control of the total circulation has significant limitations. Caution is required in interpreting such results. The dichotomy between reflex control of heart rate and that of vascular resistance after partial baroreceptor denervation and the contribution of other afferents after sinoaortic denervation are significant.

LIMITED USE OF VOLUME EXPANSION TO TEST ARTERIAL BAROREFLEXES. Both arterial pressure and cardiac filling pressure increase with expansion of blood volume and activate the arterial baroreceptors as well as cardiopulmonary baroreceptors with vagal afferents. Increases in the activity of both these groups of receptors inhibit sympathetic outflow to the circulation (347, 634). Investigators (179, 302) have used volume expansion to assess the gain of the arterial baroreflex when cardiopulmonary baroreflexes are functioning; they should consider the contribution of the cardiopulmonary baroreflex to the total response. We have observed that volume expansion reflexly decreases renal sympathetic nerve activity [Fig. 29; (621)]. After selectively interrupting sinoaortic nerves, volume expansion is associated with significant reductions in renal nerve activity, similar to those in the presence of intact sinoaortic nerves (Fig. 29). Bilateral vagotomy abolishes these decreases (621). Conversely, in the absence of vagal afferents, volume expansion causes a rise in arterial pressure that is associated with a modest decrease in renal nerve activity, no more than 30% of the decrease in the presence of intact vagal afferents (621). In the presence of all sets of inhibitory afferents, the reflex reduction of renal sympathetic nerve activity during volume expansion ap-

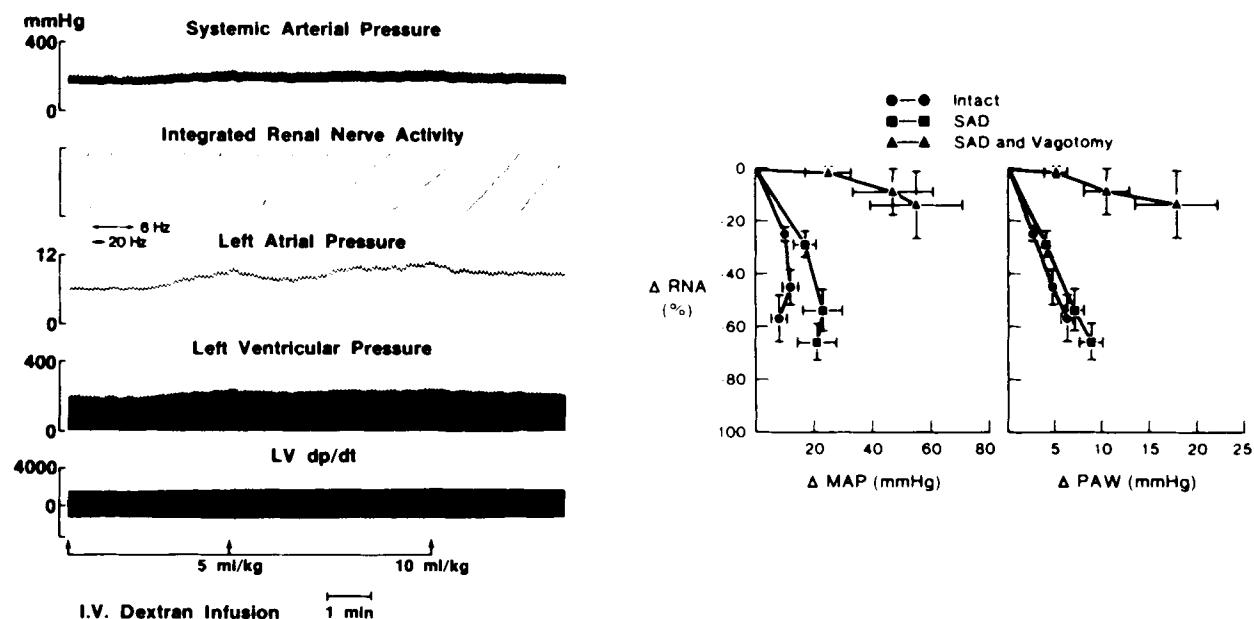


FIG. 29. *Left:* effect of volume expansion with intravenous dextran in an anesthetized dog; integrated renal nerve activity declines. *Right:* correlations between changes in renal nerve activity (Δ RNA) and mean arterial pressure (Δ MAP) or mean pulmonary artery wedge pressure (PAW) during volume expansion. Sinoaortic denervation (SAD) had a minimal effect on changes in renal nerve activity, whereas bilateral vagotomy essentially abolished reflex. [From Abboud (5) and Thames, Miller, and Abboud (621).]

pears to predominantly reflect the activity of cardiac vagal afferents. Therefore the response to volume expansion should not be used to test the integrity of arterial baroreceptors if vagal afferents are intact.

ACUTE VERSUS CHRONIC DENERVATION OF BARORECEPTOR AFFERENTS. Sequential denervation of arterial baroreceptors indicates that one remaining set of arterial baroreceptors may significantly restrain sympathetic activity and vascular tone. An important question, however, is whether chronically removing one set of arterial baroreceptors or even both sets can sustain increases in resistance and hypertension. It seems that only one set of arterial baroreceptors (aortic or carotid) can exert a normal reflex vasomotor control on hindlimb resistance during changes in arterial pressure in normotensive animals (Fig. 28). Cowley et al. (135) suggest that sectioning carotid sinus nerves in dogs does not lead to sustained elevation of arterial pressure but rather to labile hypertension. On the other hand Krieger (372) in rats, Ito and Scher (316) with bilateral aortic denervations in dogs, and Fink et al. (212) in rats suggest that sustained increases in pressure can occur after section of one set of afferents. The reason for the discrepancy may be in the degree to which the remaining sets of afferents can augment their restraint on excitatory preganglionic neurons. The potential may be limited in hypertensive animals (254). Our acute experiments suggest that this phenomenon is important (254, 255). Clearly when the input from all sets of inhibitory afferents is removed, such as with lesions of the NTS, significant hyperten-

sion develops (477). However, this is an area of debate that requires additional studies.

Sensitizing Sensory Receptors and Modulating Efferent Sympathetic Neurotransmission

In addition to the mechanisms for the CNS integration and interaction of cardiovascular reflexes, other mechanisms may partly account for the observation that changing input from one group of receptors can change the gain of another reflex, which would account in part for the interaction among cardiovascular reflexes.

SENSITIZING SENSORY RECEPTORS. The signal generated at the receptor or sensory ending may be enhanced although the stimulus to the nerve ending may remain constant.

Catecholamines. Applied directly to the carotid sinus, epinephrine or norepinephrine increases baroreceptor impulse activity and decreases the reflex fall in systemic arterial pressure (379). Applying other vasoactive drugs to this region may augment or reduce the discharge of the carotid sinus baroreceptors. Similar findings have been reported with norepinephrine in an isolated rat aortic arch preparation (246, 377). Intravenous administration of norepinephrine sensitizes aortic nerve C fibers so that they discharge at levels of pressure well below the threshold for their activation in the absence of norepinephrine (2). Sampson and Mills (550) studied 55 carotid sinus baroreceptor fibers to determine the influence of sympathetic

stimulation on the discharge of these endings. Sympathetic stimulation augmented the discharge of 27 of these 55 fibers; that of the remaining 28 was unaffected. The sympathetic nerves were stimulated in these experiments at high frequencies (4–10 Hz), probably above the physiological range. Recent reports indicate that stimulating the sympathetic nerves to the carotid sinus region reduces the diameter of the sinus at any constant pressure and that during sympathetic stimulation, firing is reduced at low pressures and increased at high pressures (505). Firing, however, is increased with respect to radius at all radii during nerve stimulation. The responses of these baroreceptor afferents were also studied under conditions of high-frequency sympathetic stimulation. Thus evidence from a variety of sources suggests that the catecholamines and high-intensity electrical stimulation of the sympathetic nerves can alter the sensitivity of the carotid and aortic baroreceptors. Therefore activating reflexes such as the somatic reflexes, which excite sympathetic discharge, and the cardiopulmonary vagal reflexes, which tend to inhibit sympathetic discharge, could alter the sympathetic outflow to the carotid sinus and aortic arch and thus increase or reduce the sensitivity of the arterial baroreceptors. However, the reflex effects of changing carotid sinus nerve activity during alterations in sympathetic drive have been mixed. In some experiments (679) electrically stimulating the cervical sympathetic nerves actually reduced the magnitude of the reflex response to carotid occlusion. This may have been due to a reduction in carotid sinus diameter rather than to a direct effect of the released norepinephrine on the nerve

endings. In contrast others found that strong stimulation of the cervical sympathetic nerves at low carotid sinus pressures causes large decreases in heart rate and blood pressure that are mediated by the carotid baroreceptors, whereas stimulation at high carotid pressures results in smaller reductions in heart rate and blood pressure (70). These findings contrast with those of Landgren and colleagues (379) and Aars and colleagues (2).

Felder, Heesch, and Thames (204) recently studied the effects of right common carotid occlusion or of raised pressure in the isolated right carotid sinus on the firing rate of the isolated left carotid sinus baroreceptors exposed to a pulsatile pressure with constant mean and pulse amplitude. Raising pressure from 50 to 200 mmHg in the isolated right carotid sinus caused reflex withdrawal of sympathetic tone and decreased sympathetic activity to the left carotid sinus region. This reduced the firing rate of the left carotid sinus baroreceptors even though the pressure stimulus to the sinus was constant. Opposite responses were seen during right common carotid occlusion in experiments in which the right carotid sinus remained in continuity with the circulation (Fig. 30). Although somewhat inconsistent the bulk of the data on the influence of the sympathetic nerves on the gain of the carotid baroreflex suggests that sympathetic activity increases the rate of baroreceptor discharge and that the physiological modulation of sympathetic drive to the carotid sinus region may modify the strain sensitivity of these baroreceptors. Several reflexes may alter sympathetic outflow to the carotid and aortic baroreceptor regions and thereby alter the sensitivity of these re-

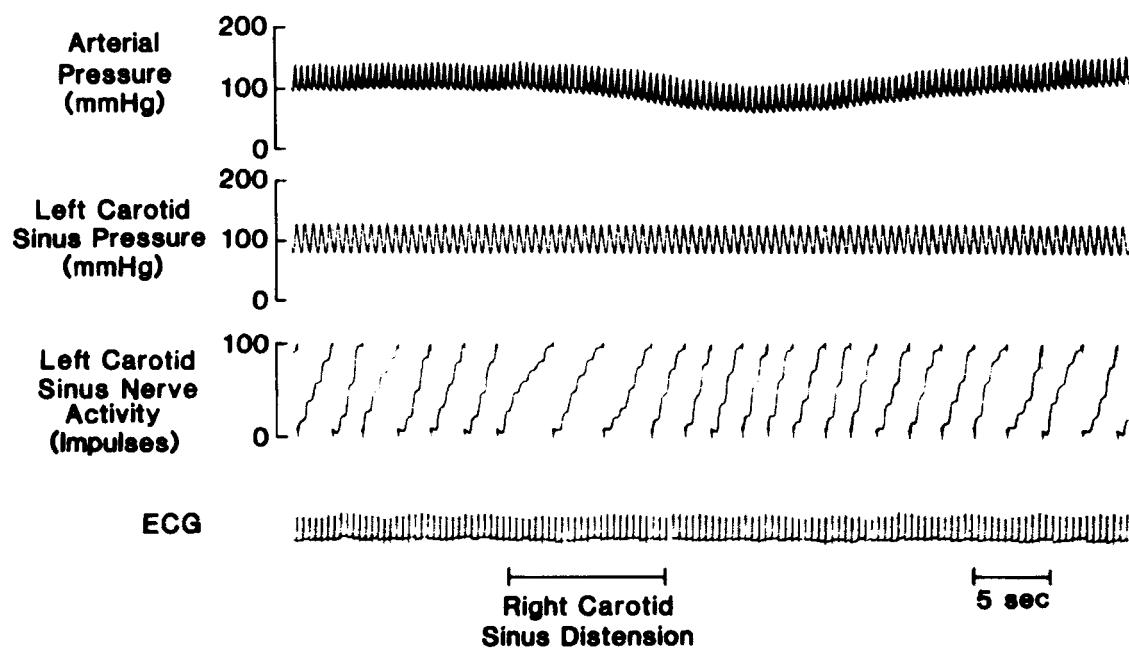


FIG. 30. Left carotid sinus nerve activity decreases despite constant distending volume and isolated left carotid sinus pressure. Decrease resulted from a reflex triggered by distending right carotid sinus, causing withdrawal of sympathetic drive. [From Felder, Heesch, and Thames (204).]

ceptors to changes in pressure. This could act as an important mechanism in altering the gain of the arterial baroreflexes.

Changes in sympathetic drive to the heart, particularly to the left ventricle, may also influence receptors in the cardiopulmonary region. Intracoronary or intravenous catecholamines, electrical stimulation of the cardiac sympathetic nerves, or reflex increases in sympathetic discharge elicited by common carotid occlusion increased the discharge of receptors in the left ventricular myocardium and epicardium for a high percentage of fibers (472, 584). Responses to intravenous epinephrine and carotid occlusion were also similar (481). Increases in left ventricular contractility resulting from isoproterenol administration augment the discharge of 50% of left ventricular mechanoreceptor C fibers and administration of propranolol reduces ventricular contractility and also the discharge of these left ventricular C fibers (632). The latter effect of propranolol results solely from effects on ventricular mechanics and is not due to the nonspecific membrane-stabilizing effects of propranolol on these C fibers (614). Similar effects have been reported for left ventricular medullated vagal afferents (256). Thus evidence from a variety of sources indicates that neurohumoral adrenergic mechanisms can augment the discharge of ventricular vagal C fibers. Increases in left ventricular contractility may augment the inhibitory influence of ventricular receptors (afferent vagal fibers) on sympathetic outflow to the periphery (223). Thus effects on ventricular mechanics can be translated directly into alterations in receptor behavior and in the gain of a cardiac (particularly ventricular) reflexes. Evidence in humans supports this view (207).

How could these effects of nerve activity and circulating catecholamines contribute to altered interactions among cardiovascular reflexes? As indicated in **MODIFYING REFLEX GAIN BY CHANGING TONIC INFLUENCE OF ONE SET OF SENSORY AFFERENTS**, p. 713, an important interaction between cardiac and sinoaortic baroreceptors in the reflex regulation of the circulation occurs under a variety of circumstances (403, 427). Removing the carotid baroreflexes augments the gain of the vagal cardiopulmonary reflex. Does the augmentation of the cardiopulmonary reflex gain reside entirely in the CNS, or could removing sinoaortic baroreceptor influences increase the sympathetic discharge of the heart, sensitize cardiac (particularly ventricular) receptors with afferent vagal fibers, and thus augment their inhibitory influence on the vasomotor centers? The gain of the carotid baroreflex is also augmented when the input from cardiac receptors is reduced (5, 6). Is this augmented gain solely the result of CNS mechanisms or could withdrawal of aortic and cardiopulmonary afferent input increase sympathetic drive to the carotid sinus, which in turn could sensitize the baroreceptors and augment the inhibitory influence from these endings? Although the physiological significance of the influence of the sympathetic nerves

on sensory endings in the heart and great vessels remains uncertain, it appears an important potential mechanism for altering the cardiovascular reflex gain and is an area in which we anticipate further investigation. The concept needs to be kept in mind during the design of future studies.

Digitalis. Other factors in addition to the sympathetic drive can modify the strain sensitivity of the baroreceptors. These include the sodium potassium adenosine triphosphatase (ATPase) activity in the region of the receptors. The postexcitatory depression phase of baroreceptor discharge after a step input of arterial pressure has been ascribed to increased sodium potassium ATPase activity in the membrane of the stretch receptors (85). Suppressing sodium potassium ATPase with ouabain increases the sensitivity of the baroreceptors by inhibiting postexcitatory depression (558). Quest and Gillis (513) first demonstrated that digitalis increases carotid sinus baroreceptor activity. These and other investigators have shown that carotid injections of ouabain or acetylstrophantidin sensitize carotid baroreceptors in the isolated carotid sinus and augment the depressor response to increased carotid sinus pressure. Ouabain added to the solution that bathes the isolated aortic arch also sensitizes the aortic baroreceptors (558). Intravenous ouabain increases the firing of atrial receptors with myelinated afferent vagal fibers and in atropine-treated cats strophanthidin gives rise to reflex bradycardia, which is mediated by carotid and aortic baroreceptors and by the vagal cardiopulmonary baroreflex (691). Epicardial or intracoronary administration of acetylstrophantidin causes reflex bradycardia and hypotension and inhibits renal sympathetic nerve activity (581, 613). These effects have a short latency and probably result from directly stimulating ventricular endings, similar to the effect of veratrum alkaloids. In addition to direct activation of nerve endings, intracoronary acetylstrophantidin sensitizes these endings to stretch by volume expansion, thereby augmenting the vagal cardiopulmonary baroreflex (626). Chronic administration of digoxin, giving rise to therapeutic blood levels of the drug, also sensitizes the cardiopulmonary baroreflexes (622) and augments the gain of cardiopulmonary baroreflexes with vagal afferents.

Cations. Receptor discharge is also modulated by altering cations in the medium (305, 313). Reducing the sodium concentration or increasing the calcium concentration elevates the threshold and decreases the sensitivity of the baroreceptors (376, 378). On the other hand increasing the potassium may reduce the threshold (31). This ionic sensitivity has been demonstrated also by the work of C. M. Heesch, M. D. Thames, and F. M. Abboud [unpublished observations; (273)] who showed that verapamil, probably by inhibiting an inward sodium current (314), decreases the baroreceptor sensitivity, whereas nifedipine, which prevents calcium entry or alters membrane-bound calcium, increases baroreceptor sensitivity (Fig. 31).

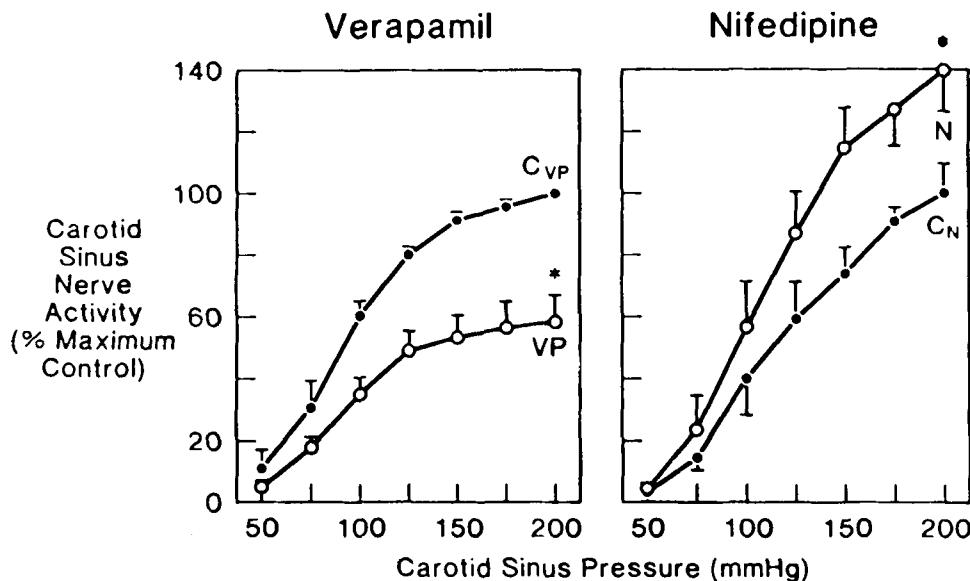


FIG. 31. Responses (mean \pm SE) of carotid sinus nerve activity during changes in carotid sinus pressure (C_{VP} , C_N) before and after exposure of the carotid sinus to verapamil (VP; 5 μ g/ml) or nifedipine (N; 10 μ g/ml). * $P < 0.05$ for difference in slope of responses. (VP, 5 dogs; N, 6 dogs.) [From Heesch, Thamés, and Abboud (273).]

MODULATING EFFERENT SYMPATHETIC NEUROTRANSMISSION. In an excellent monograph Vanhoutte et al. (652) review the modulation of norepinephrine release at the neuroeffector junction, an extremely important topic. The amount of norepinephrine released from the nerve terminals during sympathetic stimulation is modulated by various factors and retained in the synaptic cleft. The level of parasympathetic tone, for example, may influence the amount of norepinephrine released from the sympathetic nerve terminal in the region of the sinoaortic node, the atrioventricular node, or the conduction system in the heart. Because parasympathetic innervation in the conduction system is much greater than in the cardiac muscle, this interaction between the parasympathetic and sympathetic discharge is most evident with dromotropic and chronotropic responses. Other factors that determine the amount of endogenous norepinephrine available in the synaptic cleft at the receptors include its reuptake rate by neuronal and nonneuronal tissues and its metabolism. Drugs such as guanethidine, cocaine, and amitriptyline, which inhibit the reuptake of norepinephrine, and monoamine oxidase inhibitors, which prevent its metabolism, result in higher concentrations of neurotransmitter and potentiated responses to sympathetic drive.

Several biogenic amines and peptides (e.g., angiotensin, histamine, serotonin, epinephrine) and other tissue factors (e.g., prostaglandin, adenosine) also modulate its release. Several receptors have been identified pharmacologically at prejunctional sites at the sympathetic terminals. Activating these receptors may either facilitate or inhibit norepinephrine release during sympathetic stimulation.

Parasympathetic-sympathetic interaction in heart. The various sensory receptors have selective nonuniform influences on sympathetic outflow to the heart and to different parts of the circulation and on cardiac vagal motor neurons. Because the heart has a dual sympathetic and parasympathetic innervation, the potential exists for an interaction between these two arms of the autonomic system. The evidence for such an interaction is ample (288, 388, 570). Two types of interaction have been described. The first, accentuated antagonism, is based on the observation that the negative inotropic response to parasympathetic activation becomes more enhanced as the sympathetic drive to the myocardium increases. A similar interaction in terms of chronotropic effects has also been described: the magnitude of cardiac slowing in parasympathetic activation becomes progressively enhanced as the basal sympathetic drive becomes augmented. The parasympathetic drive exerts a direct negative or inhibitory influence and antagonizes the positive or excitatory sympathetic influence. This accentuated antagonism probably results from the release of two different second messengers by cholinergic and adrenergic stimuli, which have opposite effects and result in the observed responses (663).

Reciprocal excitation is another type of interaction. Activating parasympathetic cholinergic fibers to the heart increases inotropic and chronotropic states (caused by norepinephrine release from cardiac sympathetic nerve endings), probably by a direct innervation or the close proximity between the postganglionic parasympathetic neurons, which release acetylcholine, and the sympathetic nerve endings, which may be stimulated to release norepinephrine by ace-

tylcholine. However, the concept of reciprocal excitation in the heart is difficult to reconcile with the effects of acetylcholine and prejunctional muscarinic receptors on [³H]norepinephrine release from vascular segments during electrical stimulation *in vitro*. Acetylcholine in these preparations reduces the release of norepinephrine from blood vessels (652).

With these concepts in mind one can envision parasympathetic-sympathetic interactions that are involved in the neuroregulation of the heart. If, for example, one reflex was activated and induced a large increase in parasympathetic drive to the heart while at the same time the activation of another group of receptors caused a large inhibition of sympathetic outflow to the heart, then the magnitude of vagal parasympathetic influence could be underestimated (opposite of accentuated antagonism). Similarly, if the parasympathetic drive became augmented and sympathetic drive was concomitantly augmented, then the cholinergic influences would become exaggerated and thus the influence of a specific reflex on parasympathetic outflow to the heart would be overestimated (accentuated antagonism). Although an interaction between the two limbs of the autonomic system is recognized, the magnitude of its contribution to the various reflex responses has not been examined systematically.

Local modulation of adrenergic neurotransmitter release. Changes in the metabolic environment at the neuroeffector junction modulate the release of norepinephrine from the vascular segment during electrical sympathetic nerve stimulation. Similarly the naturally occurring biogenic amines such as acetylcholine, histamine, and serotonin may cause vasodilatation directly or by activating specific prejunctional receptors at the terminal to reduce the release of neurotransmitters. The vasodilatation in skeletal muscle during emotional stimuli or vasovagal syncope may result directly from activated sympathetic cholinergic pathways and indirectly from suppressed norepinephrine release from noradrenergic terminals (652).

The released neurotransmitter suppresses its own continued release through negative feedback by activating prejunctional α_2 -adrenergic receptors, which inhibit release. This important negative-feedback mechanism modulates the continued release of norepinephrine during excessive sympathetic stimulation. It may account for a gradual restoration of a lower vascular tone immediately after the sudden increase in sympathetic drive that follows partial baroreceptor denervation (255). The mechanism of inhibition of norepinephrine release through activation of prejunctional α_2 -adrenergic receptors is important in explaining the mechanism of action of certain adrenergic agonists (e.g., clonidine) in reducing arterial blood pressure and inhibiting the influence of sympathetic drive.

In contrast to activating α_2 -receptors, which prevents the release of norepinephrine, activating prejunctional β -receptors with epinephrine may facilitate the release and the blocker propranolol may inhibit it.

Activating angiotensin II receptors at the nerve endings augments the transmitter release. Zimmerman (687) in 1967 first demonstrated in animals that angiotensin facilitates the release of norepinephrine from blood vessels; Abboud (4) in humans with intra-arterial angiotensin and LBNP suggested that norepinephrine release is augmented during reflex sympathetic stimulation.

Sodium concentration in and around the noradrenergic terminal may influence the vasoconstrictor response to nerve stimulation. Reduced sodium concentration may reduce neuronal release of norepinephrine during nerve stimulation (4, 275), a mechanism that may contribute to the hypotensive effect of salt restriction in addition to other central and reflex effects.

The temperature of the blood perfusing an organ may determine vascular reactivity. Local cooling reduces arteriolar vasoconstriction, whereas cutaneous venoconstrictor responses are augmented or prolonged (20, 667, 668). Contrasting responses during nerve stimulation with those during norepinephrine infusion suggests that local cooling may reduce the quantity of norepinephrine release.

Regulating Renin and Vasopressin

Renin and vasopressin play a major role in circulatory control. Sensory afferent impulses, which in turn modulate autonomic control, partly regulate their release.

REFLEX CONTROL OF RENIN SECRETION. Three mechanisms are widely believed to mediate the release of renin from the kidney (163, 523, 651, 683). The first is the intrarenal baroreceptor mechanism that senses changes in renal perfusion pressure and that increases renin release when the renal perfusion pressure is reduced. Increasing perfusion pressure and thus augmenting the stimulus to the renal baroreceptor can prevent renin release mediated by reflex mechanisms (321). The second mechanism for renin release involves the tubular macula densa receptor, which may sense changes in sodium chloride delivery or concentration and when they are reduced may increase renin secretion. The third mechanism is renin release mediated by increases in renal nerve activity, either by directly affecting the juxtaglomerular cells, altering renal vascular resistance (thereby altering stimulus to vascular baroreceptor), or changing the distal tubular delivery of sodium chloride to the region of the macula densa. The relative roles of these mechanisms resulting from changes in renal nerve activity probably depend on the magnitude of the change in nerve activity. Very low levels of nerve activity that do not directly alter renin secretion augment renin release mediated by nonneural mechanisms (617), suggesting an interaction between neural and nonneural mechanisms in the control of renin secretion.

Carotid baroreceptors and cardiopulmonary receptors with afferent vagal fibers probably have an im-

portant reflex influence on renin secretion (180). Reflex increases in renin secretion were consistently observed during carotid sinus hypotension when renal perfusion pressure was held constant, but a rising renal perfusion pressure during carotid sinus hypotension prevented the reflex release of renin (321). This suggests an important interaction between local renal mechanisms and neural mechanisms in the control of renin secretion. Carotid baroreflex-mediated renin release can be blocked by either α -adrenergic blockade with phenoxybenzamine or β -adrenergic blockade with propranolol (509).

Just as for the carotid baroreflex, vagal cardiopulmonary reflexes can tonically inhibit renin release (426). Reductions in circulating blood volume, so small that they do not change arterial pressure (systolic or diastolic) and presumably do not alter carotid baroreceptor discharge, increase renin secretion. Bilateral vagotomy abolishes this increase, which suggests that it is caused by decreased activity of cardiopulmonary baroreceptors mediated through the afferent limb in the vagi (619). Atrial receptors (76, 685) as well as ventricular receptors with vagal afferents (615) may play a role in the reflex control of renin secretion. Recent studies in dogs with cardiac denervation (213) have been interpreted to show that cardiopulmonary receptors are not important in regulating renin release. This is an unfortunate conclusion because there is a great deal of evidence to the contrary and because other factors may explain the results. For example, volume expansion increased arterial pressure and urinary sodium excretion, which indicates alterations in the stimulus to the vascular baroreceptor and macula densa receptor mechanisms, respectively, each of which would inhibit renin release. Furthermore the neurally mediated basal renin secretion may have been so small in this study that there was little neural influence to withdraw during volume expansion.

Carotid hypotension generally fails to elicit a reflex release of renin when the vagi are intact (321) even though the carotid baroreceptors reflexly increase renin secretion when the vagi have been sectioned. Conversely, interrupting cardiopulmonary afferent vagal input with the carotid sinuses intact and in continuity with the circulation does not increase renin release (612) even though interrupting cardiopulmonary afferent vagal input increases renin secretion when the sinoaortic baroreceptors are denervated. The available evidence indicates that an important interaction between the carotid and cardiopulmonary baroreflexes in the control of renin secretion causes these differences in response. In dogs with sinoaortic baroreceptor denervation, vagal cold block (cooling vagi to 0°C) greatly increases renin secretion from the kidney (426). When the carotid baroreceptors are intact and in continuity with the circulation and the aortic nerves are sectioned, vagal cold block fails to increase renin secretion (619). If the carotid sinuses are then isolated from the circulation with sinus pressure held constant at the control systemic pressure, vagal cold block

increases renin secretion (619). Thus, by preventing the carotid baroreceptors from responding to changes in arterial pressure, which result from vagal cold block, a neurally mediated release of renin can be observed. These data conclusively show an interaction between these two reflexes in the regulation of renin secretion. The observations regarding this interaction do not determine if this interaction is simply the result of an algebraic summation of these inputs or whether changes in input from the carotid baroreceptors alter the gain of the cardiopulmonary reflex influence on renin secretion.

Conversely, if the carotid sinus pressure is reduced with renal perfusion pressure held constant and the vagi intact, renin secretion does not generally increase (321). If the vagi are sectioned or blocked by cooling, carotid sinus hypotension greatly increases renin secretion (321). Thus the cardiopulmonary baroreflex can prevent carotid baroreflex-induced increases in renin secretion. Again these data clearly show an interaction between carotid and cardiopulmonary baroreflexes in the control of renin secretion although they do not allow us to differentiate between simple algebraic summation of these inputs or changes in the gain of the carotid baroreflex induced by changing input from the cardiopulmonary baroreceptors.

Several studies deny a role for the carotid baroreceptors in the reflex control of renin secretion (59, 76, 83, 533, 559, 580), while several others affirm such a role (93, 144, 296, 321, 452, 521). The findings outlined above may provide some insight into these divergent results. Those studies that affirmed a role for the carotid baroreflex were performed with sectioned vagi and controlled renal perfusion pressure. Thus interactions between the carotid and cardiopulmonary baroreflexes and between the carotid baroreflex and intrarenal mechanisms for renin secretion may have prevented some investigators from observing increases in renin secretion during carotid sinus hypotension.

Mark, Abboud, and Fitz (433) confirmed these interactions for renin release in humans. Although several earlier studies had shown that decreased baroreceptor restraint during upright posture (88, 111, 485) or LBNP (202, 250), particularly during low sodium uptake (554), increases plasma renin activity in humans, the relative roles of arterial versus cardiopulmonary baroreceptors were not clarified. The study by Mark, Abboud, and Fitz (433) indicates that low levels of LBNP do not increase plasma renin despite a significant fall in cardiac filling pressure and reflex vasoconstriction of the forearm. Parallel findings were noted during moderate loss of blood volume in humans in that plasma renin did not rise (92, 245, 287). At higher levels of LBNP sufficient to decrease pulse pressure and cause reflex tachycardia, plasma renin levels did increase significantly; propranolol blocked that increase (433). A decrease in the restraint from both arterial and cardiopulmonary baroreceptors seems necessary for the renin response, because Mancia et al. (424) reported that selective inhibition of the

carotid restraint with neck compression did not greatly increase renin in humans. Thus in humans there may be a great deal of redundancy in the arterial and cardiopulmonary baroreflex control of renin secretion.

The CNS loci for the interaction of carotid and cardiopulmonary inputs in the reflex control of renin secretion remain unknown. However, selectively stimulating selected areas in the hypothalamus (684) and medulla (527) can respectively inhibit or excite renin release. These areas may be influenced by carotid and cardiopulmonary baroreceptors.

There is a puzzling problem regarding carotid reflex-versus cardiopulmonary reflex-mediated increases in renin secretion. Carotid sinus hypotension (with vagi sectioned) consistently increases renin secretion only if the large increases in systemic pressure are prevented from increasing renal perfusion pressure (180). In contrast, vagal cold block (after sinoaortic denervation) greatly increases renin release despite large increases in renal perfusion pressure (426). The basis for this difference is far from clear and merits further investigation.

REFLEX CONTROL OF VASOPRESSIN SECRETION. There is now strong evidence for an important role for carotid and cardiopulmonary reflexes in the control of vasopressin secretion (107, 233, 573, 575, 623, 624) and for important interactions (575, 624, 625) between these reflexes in the control of vasopressin secretion in dogs. The role of these reflexes in control of ADH secretion in humans is uncertain.

Several investigators have shown that the carotid baroreceptors tonically inhibit the release of vasopressin. After sectioning the vagal and aortic baroreceptor afferents, carotid sinus hypotension induced by carotid occlusion or hemorrhage (107, 573) or interruption of the carotid sinus nerves (624) greatly increases plasma vasopressin. Interrupting afferent vagal fibers after sinoaortic baroreceptor denervation does also (624, 625), indicating that cardiopulmonary afferent vagal fibers tonically inhibit vasopressin secretion.

The early experiments of Share and Levy (574) first suggested the possibility of an important interaction among cardiovascular reflexes in the control of vasopressin secretion. They found that carotid occlusion failed to release vasopressin unless the vagi and aortic nerves had been previously sectioned. Thames and Schmid (624) subsequently showed that after sectioning the aortic nerves, denervating the carotid sinuses failed to increase plasma vasopressin when the vagi were intact but that carotid sinus denervation after sectioning the vagal and aortic nerves greatly increased plasma vasopressin, as previously observed by Share and Levy (574). Thus the vagi alone can prevent carotid baroreflex-induced increases in ADH.

More recent studies also suggest an interaction between the carotid and cardiac receptors with afferent vagal fibers in the control of vasopressin secretion (623). Stimulating cardiac receptors with veratrum

alkaloids caused marked hypotension but no changes in plasma vasopressin despite the presence of intact arterial baroreflexes, which were expected to increase vasopressin secretion in response to the hypotension. After sinoaortic baroreceptor denervation, however, intracoronary veratrum alkaloids inhibited vasopressin secretion, as reflected in decreases in plasma vasopressin. This further suggested an interaction between cardiac and carotid reflexes in the control of vasopressin (623). After sinoaortic baroreceptor denervation and vagotomy, intracoronary injection of veratrum alkaloids unexpectedly and greatly increased plasma ADH. The many sensory endings in the heart, subserved by spinal afferent fibers and referred to as cardiac sympathetic afferents (418), and probably mediate the vasopressin increase observed under these circumstances.

Thames and Schmid (625) have systematically shown an important interaction between cardiopulmonary and carotid baroreflexes in the regulation of ADH secretion and assessed the relative influence of these groups in the regulation of ADH secretion. The changes in this secretion resulted from concomitantly induced changes in cardiopulmonary vagal input and carotid baroreceptor input. These observations support the view that the carotid baroreflex influence on vasomotor outflow to the periphery exceeds that of the cardiopulmonary baroreflex, whereas the influence of the cardiopulmonary baroreflex on vasopressin secretion equals or may even exceed that of the carotid baroreflex. Share (573) arrived at a similar conclusion in studying the responses to hemorrhage in intact dogs, in dogs with carotid denervation, and in dogs with vagi sectioned. The interpretation of those experiments is clouded because in them vagotomy also interrupted the aortic baroreceptor fibers.

Much has been written about the role of atrial receptors in regulating ADH secretion from the neurohypophysis. Goetz et al. (244) recently and extensively reviewed this area and suggested that the role of atrial receptors in controlling ADH is uncertain or at best modest. However, recent evidence suggests that cardiopulmonary receptors (which include endings in atria, ventricles, great veins, and lungs) exert a major tonic inhibitory influence on ADH secretion. Ventricular receptors may have a particularly large influence on ADH secretion (268, 623).

As outlined in **INTERACTIONS OF HYPOTHALAMUS WITH BARORECEPTORS AND CHEMORECEPTORS**, p. 689, changing input from arterial baroreceptors (456, 680, 681) or from atrial receptors (357, 457) alters the discharge of neurons in the supraoptic or paraventricular nuclei. Many of these same cells that respond to mechanoreceptor input are also sensitive to changes in plasma osmolality (457). Possibly hypothalamic neurosecretory neurons are themselves the ultimate site for integrating diverse reflex and nonneural influences on vasopressin secretion. The preliminary results of Meninger (456) support this view.

In conclusion, arterial baroreflexes, cardiopulmonary receptors with afferent vagal fibers, and possibly cardiopulmonary receptors with spinal afferent fibers may all influence the secretion of vasopressin. Interactions among these inputs may have an important influence on net vasopressin secretion. This point should be kept in mind because various interventions may simultaneously change the discharge of these receptor groups, which have directionally opposite influences on ADH secretion. The net ADH response under such circumstances might not accurately indicate the influence of a single receptor group. Interactions of cardiovascular reflexes may have made it difficult to detect a significant influence of specific receptor groups, such as atrial receptors (244), in the control of vasopressin secretion.

CLINICAL IMPLICATIONS

Interactions among several cardiovascular reflexes play an important role in determining circulatory adjustments in many physiological and pathophysiological conditions. Several of these conditions are referred to in this chapter and in the chapters by Shepherd, Rowell, Mark and Mancia, and Blix and Folkow in this *Handbook*. Integrated reflex responses may be important in humans during exercise, diving, high-altitude adaptation, emotional stress, orthostatic hypotension, vasovagal syncope, aortic stenoses, sudden-infant-death syndrome, hemorrhage and shock, hypertension, myocardial infarction, heart failure, and many other conditions. Many facets of this topic have been reviewed (5, 6, 12, 19, 216, 293, 365, 428, 575-577, 594). In this section we discuss three clinical states in which reflex adjustments may be important: myocardial infarction, heart failure, and hypertension. Many of the ideas in this section are speculative, particularly those related to heart failure and hypertension. This section is thus a group of hypotheses for the role of integrated cardiovascular reflexes in circulatory control in pathophysiological states. We think that many of these hypotheses should be tested.

Integrated Neural Responses to Myocardial Ischemia and Infarction

Myocardial ischemia and infarction change sympathetic outflow to the heart and peripheral circulation. Cardiovascular reflexes mediate many of these changes. Coronary occlusion activates sensory endings in the left ventricle with afferent vagal fibers (19, 630, 631). These endings are preferentially distributed to the inferoposterior wall of the left ventricle in dogs and possibly in humans (502, 616, 620, 666). Stimulating these endings with coronary occlusion augments their inhibitory influence on the vasomotor centers and inhibits sympathetic outflow to hindlimb (266), skeletal muscle (620, 631, 658), kidney (267, 616), and heart (134, 205).

Myocardial ischemia also activates sensory endings in the heart with sympathetic or spinal afferent fibers (72, 84, 645). In spinal cats (419) and dogs (206) increased activity from these endings during coronary occlusion increases sympathetic discharge to the heart. The influence of this spinal reflex in the control of sympathetic outflow to the heart during coronary occlusion is not evident in dogs when the spinal cord is intact (432). However, input from these endings to higher centers probably mediates the sensation of chest pain and does mediate a pseudoaffective response to coronary occlusion in lightly anesthetized cats (84). Although increases in efferent renal nerve activity that reportedly occur during coronary air embolization were thought to be mediated partly by arterial baroreceptors and partly by afferent sympathetic endings (646), the role of the latter group of receptors was not studied after sinoaortic denervation. Thames and Abboud (616) observed increases in renal nerve activity during coronary occlusion in dogs after section of the aortic, vagal, and carotid sinus nerves. Although these increases may have been mediated by sympathetic afferent fibers, it is also possible that baroreceptors in the carotid vessels but not in the sinus per se remained innervated and mediated these responses. Although such baroreceptor endings probably contribute minimally to baroreflexes under normal circumstances (sinoaortic baroreflexes intact), they may be more important after sinoaortic denervation and vagotomy (616).

The third group of sensory endings that may be important during coronary occlusion comprises the arterial baroreceptors. Changes in arterial pressure alter the discharge of these endings and thus their inhibitory influence on sympathetic outflow to the periphery. Coronary occlusion generally decreases arterial pressure in anesthetized animals and conscious dogs (63, 504), but left anterior descending coronary occlusion commonly increases arterial pressure in conscious monkeys (515) and humans (666).

One might anticipate that during coronary occlusion, interactions among the cardiovascular reflexes mediated by cardiac receptors and arterial baroreceptors would determine the net changes in sympathetic outflow to specific regional vascular beds. Substantial evidence now supports this view (5, 63, 205, 504, 616). The integrated or net responses of sympathetic outflow depend on the specific vascular bed involved, the relative influence of the various receptor groups on the sympathetic outflow to a given vascular bed, and the relative magnitude of the change in activity of each group of sensory endings (5, 616).

What are the integrated responses to coronary occlusion, and what is the contribution of each group of sensory endings? When the arterial baroreceptors were denervated so that coronary occlusion activated only cardiac sensory endings with vagal and sympathetic afferent fibers, decreases in cardiac (205) and renal (616) sympathetic nerve activity and vasodila-

tation in hindlimb and skeletal muscle (504, 620, 658) were observed. Vagotomy abolished these inhibitory responses. After sinoaortic denervation and vagotomy, coronary occlusion generally fails to elicit any reflex responses when the spinal cord is intact (205, 206, 620). Carried out with cardiac receptors and arterial baroreceptors intact, coronary occlusion causes vasodilatation in the hindlimb (probably mainly in skin) (266), but vasoconstriction in skeletal muscle (620, 658). If the circumflex coronary artery is occluded, activation of cardiac vagal afferent fibers is greater than if the left anterior descending artery is occluded. Circumflex occlusion with intact arterial baroreceptors does not change renal nerve activity, whereas left anterior descending occlusion significantly increases it, even though hypotension is greater during circumflex occlusion (616). Thus activating cardiac vagal afferent fibers during circumflex occlusion prevents arterial baroreflex-mediated increases in renal nerve activity. The responses of the efferent cardiac sympathetic nerves to coronary occlusion are between those of kidney and skeletal muscle (205). Thus cardiac sympathetic nerve activity increases during either left anterior descending or circumflex occlusion. The increases during circumflex occlusion tend to be less than those from left anterior descending occlusion despite the greater fall in arterial pressure during circumflex occlusion.

Hypotension during circumflex occlusion is probably greater because a much larger number of afferent vagal fibers are activated (616, 620), since after vagotomy left anterior descending and circumflex occlusions cause similar decreases in arterial pressure. Bishop and Peterson (63, 504) reached a similar conclusion regarding the role of vagal afferents in the hypotension accompanying coronary occlusion from studies in conscious dogs with sinoaortic denervation. There is evidence from chemical activation of the cardiac receptors with veratridine or nicotine that they are preferentially distributed in the inferoposterior wall of the left ventricle of dogs (658).

Webb et al. (666) documented that infarction of the inferior wall in humans is commonly associated with bradycardia and hypotension, while anterior wall infarction is associated with tachycardia and hypertension. The experimental observations may help us understand the pathophysiology of these different autonomic responses to myocardial infarction in humans. A preferential distribution like that in dogs, where sensory endings mediating inhibitory reflex responses to coronary occlusion are preferentially distributed to the inferoposterior wall of the heart, is present in humans. The observation that during coronary arteriography in humans a reflex bradycardia and vasodilatation are mediated through cardiac afferents supports this (189). Injecting radiographic contrast medium into the coronary artery supplying the inferoposterior wall of the heart more commonly results in bradycardia and hypotension than when contrast is

injected into the artery supplying the anterior wall (503). Furthermore inferoposterior myocardial ischemia resulting from coronary spasm is commonly associated with bradycardia and hypotension, while anterior ischemia generally eventuates in tachycardia and increases in arterial pressure (502). Assuming that cardiac receptors mediating inhibitory reflexes are preferentially distributed to the inferoposterior wall of the heart in humans, then activating these endings during myocardial ischemia or infarction may result in bradycardia and hypotension and may prevent the arterial baroreflexes from maintaining pressure at normal levels (577, 656). In contrast, during anterior wall infarction or ischemia, few of these sensory endings seem to be activated (656). However, activating pain fibers and possibly other cardiac sympathetic (spinal) afferents may elicit tachycardia and hypertension, probably by a supraspinal mechanism (206). These supraspinal mechanisms also may inhibit the arterial baroreflex, as is evident from the rise in pressure. Why don't these spinal afferents, which relay information to higher centers, mediate tachycardia and hypertension during inferoposterior ischemia? Activation of receptors mediating inhibitory responses, apparently preferentially distributed to this region of the myocardium, may elicit a powerful reflex response that inhibits not only the arterial baroreflex but also responses to spinal afferent input to higher centers.

Interaction of Reflexes in Heart Failure

Circulatory adjustments in heart failure tend to restore cardiac output and tissue perfusion. These adjustments include an increase in blood volume, an increase in peripheral venous tone, an increase in resistance in certain vascular beds, and changes in capillary surface area and permeability (17, 19).

Several mechanisms are involved in the adjustments to heart failure: humoral factors (renin, angiotensin, aldosterone, ADH), the sympathoadrenal system, cardiovascular reflexes, and structural and biochemical changes in heart and blood vessels. These mechanisms may vary in importance depending on the model of heart failure used (left vs. right failure) or the duration and severity of the disease. This section discusses the role of neurohumoral factors and neurogenic reflexes.

HUMORAL FACTORS: RENIN, ANGIOTENSIN, ALDOSTERONE, AND ANTIDIURETIC HORMONE. In 1946 Merrill et al. (458) and in 1963 De Champlain et al. (166) reported increased renin and angiotensin levels in patients with chronic heart failure. The role of this system in the circulatory adjustments to heart failure was recently examined in two different experimental models (470, 664).

Morris et al. (470) studied the humoral and hemodynamic changes in congestive heart failure produced in the rabbit during a period of 2–12 days after aortic constriction. They demonstrated that a suprarenal constriction of the abdominal aorta and daily supple-

mental sodium chloride progressively increased left ventricular end-diastolic pressure, fluid and sodium retention, ascites, and pulmonary congestion over a period of several days. Plasma renin activity and angiotensin and aldosterone concentrations also increase. In this preparation the aldosterone levels rise despite the sodium load, suggesting an altered regulatory mechanism for the renin-angiotensin-aldosterone system in heart failure.

Watkins et al. (664) evaluated the role of the renin-angiotensin-aldosterone system in congestive heart failure over a 2-wk period in conscious dogs after either pulmonary arterial or thoracic inferior vena caval constriction and examined the temporal relationship between circulatory adjustments and the renin-aldosterone system. The authors detected two phases. During the first, plasma renin activity, angiotensin II generation, and plasma aldosterone increase, whereas arterial pressure and cardiac output are low. In the second phase, retention of sodium and water and the resulting hypervolemia increase atrial and arterial pressures, which then suppress the renin-angiotensin-aldosterone system. In this second phase, the animals are edematous, have venous congestion and ascites, and have reached a new steady state of sodium balance. This steady state may not be analogous to human chronic congestive failure, however, where renin-angiotensin secretions and often aldosterone secretions are increased despite hypervolemia (166, 239, 458).

On the basis of the two studies by Morris et al. (470) and Watkins et al. (664), as well as other studies in chronic heart failure (166, 239, 251, 289, 458, 470, 664), we suggest a temporal sequence in heart failure (19) that includes 1) a phase of increased sympathoadrenal and renin-angiotensin drive resulting from a lowered cardiac output; 2) a phase of compensatory hypervolemia, which tends to suppress the sympathetic drive and the renin-angiotensin system; and 3) in late heart failure an increase in sympathoadrenal drive and in renin-angiotensin levels possibly resulting from impairment of the restraining influence of the cardiac and arterial baroreceptor afferents.

Angiotensin and sodium retention in heart failure of short duration. Administering angiotensin converting-enzyme inhibitor in the early phases of heart failure causes persistent hypotension and reduces the ability to conserve sodium and water (664). Converting-enzyme inhibitors were ineffective, however, in the second phase of heart failure after hypervolemia had been established and the renin-angiotensin system suppressed (664).

Davis et al. (164), who gave the angiotensin II receptor blocker saralasin to dogs with thoracic caval constriction, also demonstrated the importance of angiotensin in the maintenance of arterial pressure in the low output state. Arterial pressure fell and renin levels increased, but aldosterone secretion markedly decreased.

Although reduced glomerular filtration rate may cause sodium retention, experiments in both dogs and humans indicate that this mechanism does not explain the sodium retention in heart failure (48, 74). Other factors, including sympathetic activity to the kidney, must contribute to sodium retention.

The renin-angiotensin-aldosterone system in patients with chronic failure. Although a low cardiac output may stimulate the renin-angiotensin system, there are several unusual features of this system in chronic congestive failure in humans. For example, sodium deprivation and diuresis, which ordinarily increase angiotensin and aldosterone secretion, have the opposite effect in patients with heart failure (239). Conversely the administration of salt to patients in congestive failure paradoxically increases aldosterone secretion (382). The magnitude of the rise in aldosterone may vary in different types of heart failure (677). Higher levels were found in the majority of patients with right-sided failure (677), and angiotensin infusions given to patients with congestive failure have little or no effect on aldosterone secretion either before or after diuretic therapy (350).

The regulation of the renin-angiotensin-aldosterone system in chronic failure is complex and may involve neural and humoral stimuli that vary with the types and duration of heart failure and are determined by neural impulses arising in cardiac as well as arterial or pulmonary baroreceptors. These inputs, which ordinarily restrain the neurohumoral drive for renin secretion, may be impaired or suppressed in heart failure and may contribute to the exaggerated neural drive.

Thirst and edema of congestive failure. Constriction of the thoracic inferior vena cava in dogs increases water intake and plasma extracellular fluid volume (515). Saralasin markedly reduced the water intake in two dogs in congestive failure. As recently shown angiotensin may induce thirst through a central hypothalamic action and may also cause the release of vasopressin (299). Excessive fluid intake and retention in heart failure may be mediated in part through a central action of angiotensin.

A striking increase in plasma ADH activity has been reported in dogs with congestive failure and ascites 3–17 wk after tricuspid ablation (51). The ADH did not increase in dogs without ascites. The animals had markedly positive water and sodium balances, but the changes in plasma aldosterone and in norepinephrine activity were not consistent and did not correlate well with symptoms of congestive failure. Antidiuretic hormone may play a role in the formation of ascites and edema late in congestive failure.

Persistent antidiuretic hormone release in late heart failure. The regulation of vasopressin release has been discussed in detail in REFLEX CONTROL OF VASOPRESSIN SECRETION, p. 726. Regardless of the state of hydration, plasma osmolality, or arterial pressure, an increase in left atrial distension or pressure restrains and suppresses plasma ADH (571, 573, 575).

Conceivably in late heart failure cardiac receptors have reduced sensitivity and increased threshold, possibly because of chronic stretch of the left atrium and structural changes in its wall (251, 686). The reduced activity of cardiac receptors removes a restraining influence on the secretion of ADH in congestive failure. High levels of ADH may contribute to but are not essential for the development of edema, because dogs with lesions of the neurohypophysis and diabetes insipidus do develop edema and ascites with caval constriction (265).

SYMPATHETIC AND PARASYMPATHETIC INNERVATION. Roskoski, Schmid, Abboud, et al. (537, 538, 560, 561) assessed autonomic activity in various models of heart failure by determining biochemical indices of this activity, including norepinephrine turnover rates, tyrosine hydroxylase, and choline acetyltransferase activity in the heart, blood vessels, and sympathetic ganglia.

Cardiac efferent innervation. Soon after pulmonary arterial constriction in guinea pigs, norepinephrine turnover increased in the right ventricle, possibly associated with an increase in cardiac sympathetic activity (17, 561). Later in heart failure, norepinephrine turnover in the myocardium decreased and norepinephrine depletion became more apparent, as reported previously (105, 508, 592).

With respect to the parasympathetic innervation in the myocardium there is no significant reduction in total activity of choline acetyltransferase, in contrast with the marked reduction in tyrosine hydroxylase activity (539). Thus parasympathetic innervation of the heart in failure is protected compared to the sympathetic innervation.

Similar effects were observed in the guinea pig with supravalvular aortic constriction and left ventricular hypertrophy and failure. The net turnover of norepinephrine was increased initially in the stressed left ventricle, but left ventricular failure like right ventricular failure was associated with a decrease in myocardial sympathetic innervation.

In the myopathic hamster the dysautonomia in the myocardium is different than in pressure-induced hypertrophy. Tyrosine hydroxylase activity as well as norepinephrine turnover are preserved or increased, and the increase persists until the animals die. In contrast the choline acetyltransferase activity is significantly reduced, reflecting damage to the parasympathetic postganglionic innervation in hamster cardiomyopathy (561, 589). The mechanisms responsible for the selective abnormalities in sympathetic or parasympathetic innervations in pressure-induced hypertrophy and cardiomyopathy are not clear. In the myopathic condition excessive cardiac sympathetic activity, manifested by a high norepinephrine turnover unopposed by parasympathetic inhibitory influence, may contribute to the myocardial necrosis (589, 591). The protective and beneficial effect of propranolol in

genetic cardiomyopathic hamsters supports this notion (323).

Altered sympathetic innervation and responsiveness of peripheral blood vessels in heart failure. Studies in various models of heart failure indicate that there is no consistent or uniform norepinephrine depletion in the periphery in heart failure (269, 371, 562) despite depletion of myocardial catecholamines. Furthermore convincing data indicate overactivity of the peripheral adrenergic system during the stress of exercise in heart failure. Schmid, Abboud, et al. (562) contrasted the level of adrenergic tone to the peripheral vessels in different models of heart failure in the guinea pig. Increased efferent sympathetic activity occurs in pressure-induced left heart failure caused by supravalvular aortic constriction, which may be related to the reduced activity of arterial and cardiac baroreceptors. Increased reactivity to catecholamines may also increase adrenergic influences, even when sympathetic activity is normal, as in experimental models of right heart failure with constriction of the pulmonary artery (451). In cardiomyopathic hamsters, however, there is evidence of impaired vascular reactivity to catecholamines and to sympathetic nerve stimulation in the hindquarters (439) and evidence of normal neurogenic control of the spleen (589). Thus the alteration of neurocirculatory control of the heart and peripheral circulation in myopathic disorders is quite different from that in pressure-induced hypertrophy. Measurements of catecholamine content of blood vessels in the dog showed that in right-sided failure there are normal vascular levels despite significant depletion of catecholamines in the heart (561). Others found a slight decrease in norepinephrine content of the carotid artery and thoracic aorta, no change in femoral, saphenous, mesenteric, or renal arteries, and an increase in mesenteric veins (269).

After eliminating neurogenic and humoral contributions to vascular tone, a certain degree of increased vascular resistance in humans during congestive failure remains, which may be ascribed to structural changes in blood vessels possibly related to sodium and water retention (686). These changes may explain the limited vasodilator capacity in heart failure and the reduced permeability-surface area product (257, 383, 686).

CARDIOVASCULAR REFLEXES. Evidence suggests that in heart failure the two major sensory inhibitory inputs to sympathetic drive (i.e., arterial baroreceptors and cardiopulmonary sensory afferents) may be suppressed. This results in a disinhibition of sympathetic activity and an increase in sympathetic tone.

To explain the involvement of cardiovascular reflexes in heart failure and their role in circulatory adjustments, which occur early and late in this syndrome, we propose the temporal sequence of three phases (17, 19) referred to in **HUMORAL FACTORS**, p. 728. The initial response to phase I is one of increased

neurohumoral drive caused by reductions in arterial pressure (constriction of ascending aorta) or in left atrial and left ventricular distending pressures (pulmonary artery constriction), which result in decreased activity of arterial and/or left ventricular sensory endings.

Soon after this initial phase, however, blood volume increases and arterial and left atrial pressures return to control levels. The hypervolemia of phase II causes cardiac enlargement and activates the sensory endings, which suppress the neurohumoral drive (664). Phase II must be transient, however, because numerous observations in animals and humans indicate that in chronic heart failure the sympathoadrenal and renin-angiotensin-aldosterone systems are actually activated and contribute to peripheral vasoconstriction and sodium retention. A third phase may therefore account for the excessive neurohumoral drive in chronic heart failure. Phase III, which occurs late in heart failure, may be caused by loss of activity of cardiac and arterial baroreceptors and result in increased neurohumoral drive.

This temporal sequence may explain discrepancies in results obtained in the different models of heart failure used by various investigators and examined at various phases of circulatory adjustments.

Arterial baroreceptors in heart failure. Higgins et al. (289) demonstrated that, in conscious dogs with right-sided failure produced by tricuspid avulsion and progressive pulmonary stenosis, the baroreflex-mediated bradycardia induced by a rise in arterial pressure with phenylephrine is markedly inhibited. Eckberg et al. (187) reported that patients with heart disease have a markedly suppressed reflex bradycardia, ordinarily seen during the rise in arterial pressure with an infusion of phenylephrine. Vatner and Murray (655) have also reported that bilateral carotid occlusion causes a smaller increment in arterial pressure, heart rate, and mesenteric and renal resistances in animals with heart failure compared to normal animals. Because of the integrity of sympathetic innervation to blood vessels and of the parasympathetic supply to the heart in heart failure, the defect in the baroreflex may be either in the afferent limb of the reflex or in the CNS, the latter possibly resulting from an interaction with other afferent inputs.

Functional arterial baroreceptor denervation could explain the increased sympathoadrenal drive to the peripheral circulation, but no systematic attempts to quantitate this abnormality in various types and various phases of heart failure have been made.

Cardiac sensory afferents in heart failure. Several physiological and pathophysiological states are associated with either increased or decreased activity of these afferent nerves. This and other chapters in this *Handbook* describe these situations. Increased activity occurs in the supine position during elevation of the legs and acute hypervolemia, aortic stenosis, coronary arteriography, and coronary occlusion. The car-

diovascular response is inhibitory with bradycardia, vasodilatation, and decreased sympathetic efferent activity.

Decreased activity of cardiac afferents occurs in the upright position, during pooling of blood in the lower extremities and hemorrhage, in congestive heart failure, and possibly in hypertension with left ventricular hypertrophy. The resulting cardiovascular response is excitatory with tachycardia, vasoconstriction, increased sympathetic efferent activity, and increased renin and ADH.

There is electrophysiological evidence of decreased cardiac afferent activity in heart failure. Greenberg et al. (251) studied dogs with low-output failure, and Zucker et al. (690) studied dogs with aortocaval fistula and high-output failure. Both groups showed that increases in central venous and left atrial pressures during blood volume expansion increase the discharge of afferent vagal fibers, but the frequency of discharge was suppressed significantly in heart failure (Fig. 32). The functional consequence of decreased activity of cardiac afferent nerves is an increase in neurohumoral drive.

Importance and consequences of impairment of cardiovascular reflexes in heart failure. Impaired reflexes can elicit important clinical and physiological adjustments.

Increased neurohumoral drive in heart failure. Several studies indicate an excessive neurohumoral drive in heart failure. In dogs with chronic heart failure and edema from tricuspid insufficiency and pulmonary stenosis, plasma renin activity (269) and plasma ADH levels (51) are increased. Peripheral vasoconstriction of the mesenteric and iliac vascular beds at rest is also significant (655). Humans with heart failure may have increased circulating levels of norepinephrine (105), increased plasma renin activity (239, 387), increased levels of angiotensin (166, 239), and exaggerated vasoconstrictor tone (686). Several experiments in the literature also indicate that removing cardiac vagal afferents increases neurohumoral excitation. These are reviewed extensively in *Cardiac Receptors With Afferent Vagal Fibers*, p. 697 (393, 421, 422, 434, 472, 499, 584, 612-614, 616, 618, 619, 623, 626, 627, 633, 685). Thus reduced cardiac baroreceptor afferent activity in heart failure may explain the increased neurohumoral drive.

Augmented excitatory response to exercise in heart failure. Activating somatic afferent nerves during exercise increases sympathoadrenal drive manifested by increased plasma norepinephrine concentration and reflex vasoconstriction in the nonexercising part of the circulation. The sympathoadrenal drive of exercise is markedly augmented in heart failure. Plasma norepinephrine levels during exercise are greater in patients with heart failure than in normal subjects (105). Wood (678) reported that patients with heart failure had a significant increase in forearm venous tone during mild leg exercise, whereas patients who had recovered

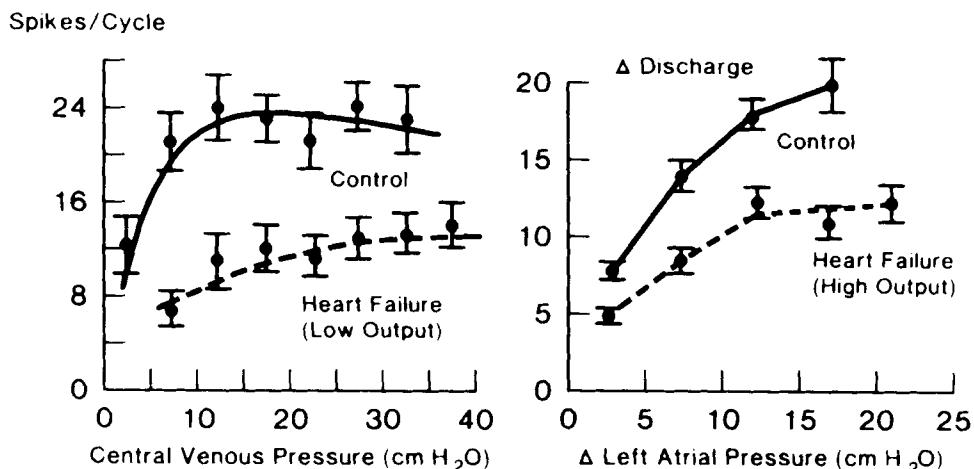


FIG. 32. Activity of atrial vagal afferents during volume expansion in control dogs (solid lines) and dogs in heart failure (dashed lines) in correlation to central venous pressure (241) and left atrial pressure (690). The afferent activity is markedly impaired in heart failure. [Adapted from Greenberg et al. (251), by permission of the American Heart Association, and Zucker et al. (690).]

from congestive failure had no increase in venous tone. Ganglionic blockade inhibited the increase in venous tone. In normal subjects severe supine dynamic leg exercise significantly decreases total peripheral resistance (611), reflecting the combined effect of marked metabolic vasodilatation in the exercising lower limbs and the minimal vasoconstriction in the nonexercising parts of the peripheral circulation (544, 577). In patients with heart failure (ejection fractions <30%) supine leg exercise does not reduce total vascular resistance and forearm vascular resistance increases by 36%. The lack of a reduction in total peripheral resistance is probably caused by an augmentation of reflex vasoconstriction in the nonexercising parts of the circulation, which offsets the local dilator response in the exercising muscle. Intense renal (459) and mesenteric sympathetic vasoconstriction in dogs with heart failure during exercise far exceeds the response in normal animals (655).

The response to exercise is augmented in heart failure, and there is evidence that the somatic excitatory reflex may be exaggerated because of decreased input from arterial and cardiopulmonary baroreceptors. The somatic reflex is markedly augmented in dogs when the input from arterial or cardiopulmonary baroreceptors is reduced (5, 437, 615). A similar interaction between the inhibitory arterial and cardiopulmonary baroreceptor afferents and the excitatory somatic reflex is present in humans (657). In normal subjects isometric handgrip exercise triggers vasoconstriction in the nonexercising limbs; this vasoconstriction is markedly augmented in the presence of LBNP, which decreases the sensory input from arterial and cardiopulmonary baroreceptor sensory afferents. A similar interaction may occur in heart failure to account for the augmented vasoconstrictor responses to exercise (Fig. 33).

Paradoxical responses to upright tilt and to sodium

restriction in heart failure. When normal subjects are tilted from the supine to the upright position, plasma levels of norepinephrine increase (387) and forearm vessels constrict (8). In patients with heart failure, however, the blood levels of norepinephrine do not increase (387) and forearm vessels may dilate during upright tilt (78). De Champlain et al. (166) and Genest et al. (239) reported another paradoxical response. Sodium restriction and diuresis increase renin and angiotensin levels in normal subjects, but they significantly decrease those levels in patients with heart failure. How can one explain this? Our explanation takes into consideration the change in ventricular compliance (17). The diastolic compliance curve is abnormal in heart failure with cardiac enlargement, as indicated by rapid and large increases in filling pressure as volume increases. A change in position from supine to upright may not only cause a small reduction in diastolic volume, but it may also shift the pressure-volume relationship of the ventricle to a flatter portion of the compliance curve, i.e., a position of greater compliance, resulting in a significant fall in end-diastolic pressure and wall tension (19). This should reduce the work necessary for generating systolic tension and thus permit greater shortening for the same contractile state. Furthermore decreased diastolic tension may improve myocardial diastolic perfusion and reduce oxygen demand. Greater shortening may activate the ventricular sensory endings that discharge during systole with a frequency that depends on the mechanics of ventricular contraction (256, 618, 633). In normal subjects the upright position would also tend to decrease diastolic volume, but ventricular compliance does not change as drastically and the end-diastolic pressure and tension may decrease only slightly. The resultant force of contraction and shortening may not change or may decrease because of the Frank-Starling mechanism. Thus, although the upright position in

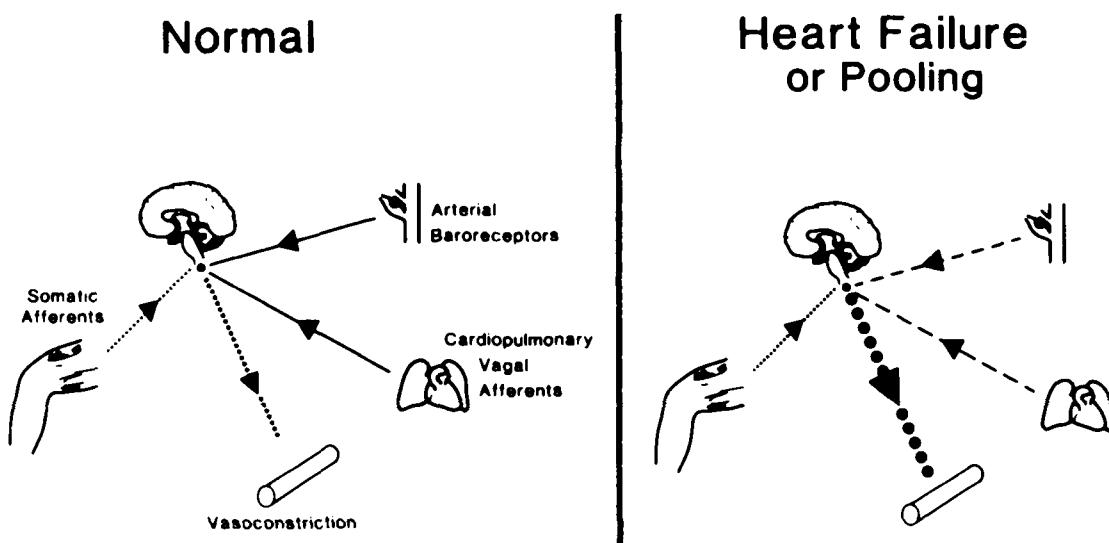


FIG. 33. Interaction between somatic afferents and arterial and cardiopulmonary afferents. Reflex vasoconstrictor response to activating somatic afferents is augmented when inhibitory input for arterial and cardiopulmonary receptors is impaired. [From Abboud, Thames, and Mark (19).]

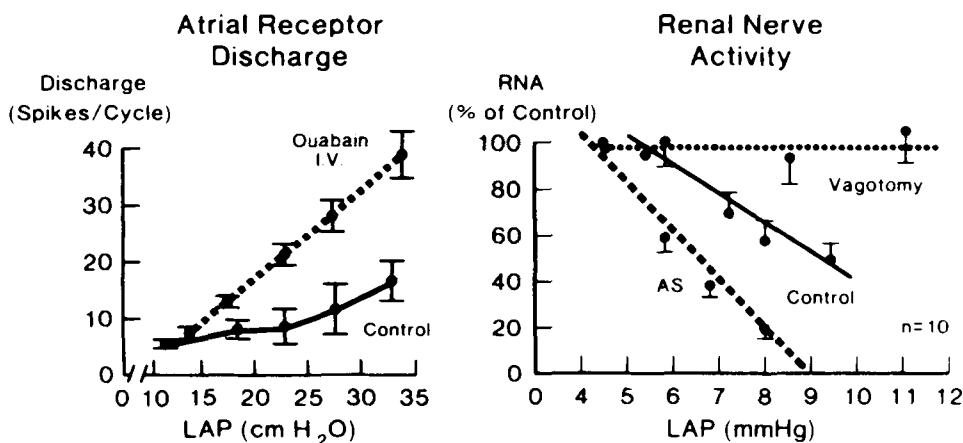


FIG. 34. Ouabain enhances atrial receptor discharge during volume expansion for similar levels of left atrial pressure (LAP) (691). Acetylstrophanthidin (AS) in coronary arteries enhances reflex inhibition of renal efferent nerve activity in anesthetized dogs for equivalent level of LAP. No inhibition is seen after bilateral vagotomy. [Adapted from Thames, Waickman, and Abboud (626) and Zucker et al. (691).]

normal subjects may decrease the activity of cardiac vagal afferents, we postulate that the opposite may occur in heart failure.

Some data in the literature are consistent with this view. Litchfield et al. (402) obtained data during supine and upright leg exercise in patients with left ventricular ejection fractions of less than 30%. During upright exercise, wedge pressure decreased significantly [18 ± 6 (mean \pm SE) mmHg in upright vs. 33 ± 3 mmHg in supine] and stroke volume increased significantly (104 ± 12 ml vs. 76 ± 6 ml), in contrast to supine exercise. The marked increase in stroke volume and reduction in wedge pressure in upright as compared to supine exercise imply a pronounced increase in the ejection fraction. This increase in ejection fraction when coupled with the greater increase in heart

rate during upright exercise (130 ± 10 beats/min vs. 115 ± 9 beats/min) may represent a significant mechanical stimulus for cardiac sensory endings that could restore their activity and reduce the reflex vasoconstrictor response to exercise in the upright position.

Sensitizing sensory endings by digitalis and nifedipine in heart failure. The beneficial effects of digitalis in heart failure may be related in part to a reflex reduction in peripheral vascular resistance and a reduction in sympathetic nerve activity to the kidneys, leading to renal vasodilatation, diuresis, and natriuresis with decreases in renin secretion. This reflex response could result from sensitization of cardiac afferent nerves or arterial baroreceptors [Fig. 34; (85, 513, 558, 581, 613, 622, 626, 691)].

Recently Heesch, Thames, and Abboud (272, 273)

demonstrated that nifedipine may increase the sensory afferent activity of arterial baroreceptors as well as the cardiac sensory afferents, resulting in a greater inhibition of renal nerve activity either with a rise in arterial pressure or with volume expansion. These experiments suggest that administering nifedipine may reduce peripheral sympathetic drive in heart failure on a reflex basis by restoring some of the sensitivity of the two inhibitory sensory afferents.

However, no data indicate that, in models of heart failure, sensitization of the sensory afferents is an important determinant of the reduced sympathetic drive during therapy with diuretics, digitalis, or nifedipine.

Reflex Interactions in Hypertension

Sympathetic innervation of blood vessels may increase vascular resistance by releasing the neurotransmitter, affecting membrane potential of vascular muscle (314), or increasing the rate of synthesis of contractile proteins (652). A reduced baroreceptor sensitivity and disinhibition of excitatory neurons, which may be acquired or may reflect a more generalized genetic membrane abnormality, may increase sympathetic activity. The increased sympathetic may be expressed more readily under certain environmental conditions, such as increased sodium intake.

Afferent impulses from groups of sensory receptors in the cardiovascular system modulate sympathetic preganglionic neurons. The role of afferents in three such areas in hypertension is discussed next: arterial baroreceptors, cardiopulmonary baroreceptors, and renal afferents.

ARTERIAL BARORECEPTORS. Eliminating the sensory input from the carotid sinus or aortic depressor nerves increases sympathetic drive and causes labile or sustained hypertension (98, 178, 477). Is the decreased sensory input from baroreceptors a causative factor in hypertension, important for its initiation rather than simply its maintenance? To answer this we must be able to detect impaired arterial baroreflexes before the onset of hypertension.

Impaired arterial baroreceptors. Ample evidence suggests that arterial baroreceptors are reset in hypertension and that they have a higher pressure threshold and reduced sensitivity to increases in pressure (1, 21, 32, 56, 87, 98, 252, 372, 447, 582). Sympathetic activity recorded from peripheral nerves in hypertensive humans is sustained despite the elevated arterial pressure (599, 660), in contrast to normotensive humans in whom the activity is suppressed with a rise in pressure.

Data from four separate experiments suggest that an abnormal baroreflex may precede or coincide with the onset of mild hypertension. In the early stages of spontaneous hypertension in the Okamoto strain of rats, the sensitivity of aortic baroreceptors is reduced significantly (85, 87). The Dahl salt-sensitive rats also have impaired baroreflexes on low sodium intake in

the absence of hypertension (249). Partial resetting of baroreceptors may occur in the absence of structural changes (556), and a significant impairment of baroreflexes may occur in the early stages of labile essential human hypertension (606).

An inherited membrane abnormality in sodium permeability and/or sodium potassium ATPase could possibly augment the phase of postexcitatory depression of the baroreceptor discharge after a step input of pressure (85) and contribute to an upward resetting and an increase in the threshold for NTS neuron activation or sympathetic neuron inhibition.

Other factors that may change the sensitivity of baroreceptors are discussed in **SENSITIZING SENSORY RECEPTORS**, p. 720; their relevance to the hypertensive state is not clear.

Central modulation of the arterial baroreflex. Baroreflexes may be impaired because of a change in input from various suprabulbar or other CNS neuronal groups to the NTS and to neurons in the reticular formation in the medulla, which in turn modulate preganglionic efferent autonomic neurons (374). Stimulating the paraventricular and supraoptic nuclei in the hypothalamus causes hypertension and tachycardia and inhibits the reflex bradycardia caused by carotid but not by aortic nerve stimulation (94, 106). In this context the contribution of emotional stress to the hypertensive state through activation of hypothalamic nuclei should be considered.

Brody, Gordon, et al. (80, 248) have shown that a lesion of the anteroventral portion of the third ventricle in the anterior hypothalamus of the rat can reduce or prevent the hypertensive state in several different models of hypertension (except in the spontaneously hypertensive strain). This area, which is also involved in the control of drinking (90, 91) and the release of vasopressin (325) and possibly of a natriuretic factor, must play an important permissive role in the increased sympathetic drive in the various models of hypertension. The afferent signals for its engagement in the hypertensive states may be humoral (324), for example, angiotensin, or neural, possibly from renal afferents (80, 95). Its effectiveness in a variety of hypertensive states emphasizes the role of the CNS regardless of the initiating factor in hypertension.

Variation in neuropeptides or biogenic amines may also alter reflexes; for example, angiotensin, Leu-enkephalin, and substance P cause hypertension and suppress baroreflexes (230). Lesions of the A2 group of adrenergic neurons that supply the NTS cause labile hypertension and also selectively inhibit the reflex bradycardia during activation of the arterial baroreflex (610).

Chalmers (101) reviewed the role of brain amines in various models of experimental hypertension. In the rat, DOCA-salt hypertension selectively decreases norepinephrine turnover in the central neurons in the medulla and increases the turnover of norepinephrine in the heart. Thus catecholaminergic nerves in the

brain stem, which normally inhibit sympathetic drive, apparently play an important role in DOCA-salt hypertension. In contrast the central catecholaminergic nerves may play a role in initiating hypertension in spontaneously hypertensive rats (SHR) but not in maintaining the elevated pressure (211, 261). Central serotonergic nerves may be more important in SHR (322). In renal hypertension destruction of central catecholaminergic nerves with 6-hydroxydopamine injected into the CNS completely prevents the development of hypertension in rabbits (211, 391). Furthermore the hypertensive response to injections of angiotensin into the lateral ventricle is markedly reduced by intracisternal administration of 6-hydroxydopamine (391). The link between the kidney and the central catecholaminergic nerves may well lie in a central action of angiotensin (208, 601). Another link between the damaged ischemic kidney and the CNS may be through renal afferents (95). The role of these afferents is discussed in **RENAL AFFERENTS**, p. 736.

Propranolol and clonidine are effective antihypertensive drugs that lower arterial pressure through a central action on catecholaminergic neurons. Propranolol blocks β -receptors and clonidine activates α_2 -adrenergic receptors; both inhibit sympathetic drive and may restore the baroreceptor sensitivity in hypertension (583, 603).

Differential control of heart rate and resistance in hypertension. Rabbits with renal hypertension of 6-wk duration have a suppressed baroreflex control of heart rate, whereas the baroreflex control of hindlimb vascular resistance and lumbar sympathetic nerve activity is preserved (254). This differential control is observed when all arterial baroreceptors are intact. A similar selective suppression of baroreflex control of rate with preservation of reflex control of hindlimb resistance is seen in normotensive rabbits after partial baroreceptor denervation of either the aortic depressor nerve or the carotid sinus nerves (255). Thus hypertensive rabbits behave as if the baroreceptor afferents were partially denervated (254, 255). When the aortic or the carotid afferents are sectioned in the hypertensive rabbits, the baroreflex control of vascular resistance and lumbar sympathetic activity is markedly inhibited, whereas in the normotensive rabbits these reflex responses are preserved (254, 255). Possibly the excitability of sympathetic neurons or preganglionic sympathetic neurons is excessively elevated in hypertension, requiring the inhibitory influence of all baroreceptor inputs. It is also possible that the degree of redundancy in the convergence of baroreceptor afferents on preganglionic sympathetic neurons is more restricted in hypertension than in normotension (255).

One cannot predict the status of baroreflex control of the total circulation just by evaluating the reflex control of heart rate. Furthermore preserving reflex control of vascular resistance in the early phases of hypertension may be protective and prevent acceleration of the hypertension, assuming of course that the

baroreflex control of vascular beds other than that of the hindlimb is preserved in this as well as other models of hypertension. Preliminary data indicate that baroreflex control of sympathetic outflow to vascular beds other than the hindlimb may not be preserved (M. D. Thames and B. N. Gupta, unpublished observation). In a study of the carotid baroreflex in hypertensive humans, the reflex control of total peripheral resistance appeared preserved or even augmented (423).

CARDIAC AFFERENTS. As described in *Cardiac Receptors With Afferent Vagal Fibers*, p. 697, activating these receptors not only suppresses sympathetic drive (19) but also changes the gain of the arterial baroreflex so that during carotid hypotension, for example, the anticipated increase in sympathetic activity is suppressed when cardiac afferent activity is increased and vice versa [Fig. 35; (656)]. The studies of their role in hypertension have been limited (209, 345, 432, 435, 529, 636).

Increased cardiac afferent activity in early human hypertension. In various models of hypertension the arterial baroreflex may be suppressed, causing a neurogenic increase in vascular resistance unless the input from the cardiac afferents is augmented. In that case the anticipated increase in sympathetic activity would be partly suppressed. To study the role of cardiac afferents in humans, blood is pooled in the lower extremities with an LBNP box. This decreases cardiac filling pressure, unloads the cardiac receptors, decreases their sensory input, and results in reflex vasoconstriction (689). An important question is whether in hypertensive humans the activity of cardiac afferents is increased, thus suppressing sympathetic tone, or decreased, thus contributing to a high sympathetic drive and vascular resistance. If increased, LBNP should augment the reflex vasoconstrictor response, whereas the vasoconstrictor response to LBNP should be reduced if the activity is decreased. The results indicate that LBNP causes greater vasoconstriction in patients with borderline hypertension than in normotensive subjects (432, 435). This effect could not be ascribed to increased vascular reactivity (435). In borderline hypertension the arterial baroreflex apparently is impaired, but the exaggerated cardiac afferent activity helps to offset the influence of impaired arterial baroreceptor activity on vascular resistance. The protective influence is most pronounced in the supine position. In the upright position, just as during LBNP, the sympathoadrenal drive may be excessive. As a corollary, renin levels increase markedly in the upright position in patients with borderline hypertension in contrast to normotensives (674).

Decreased cardiac afferent activity in animal models of hypertension. In renal hypertensive dogs and SHR, activity of afferent vagal cardiac C fibers is decreased during either transient aortic occlusion or volume expansion (345, 636). For equivalent increases

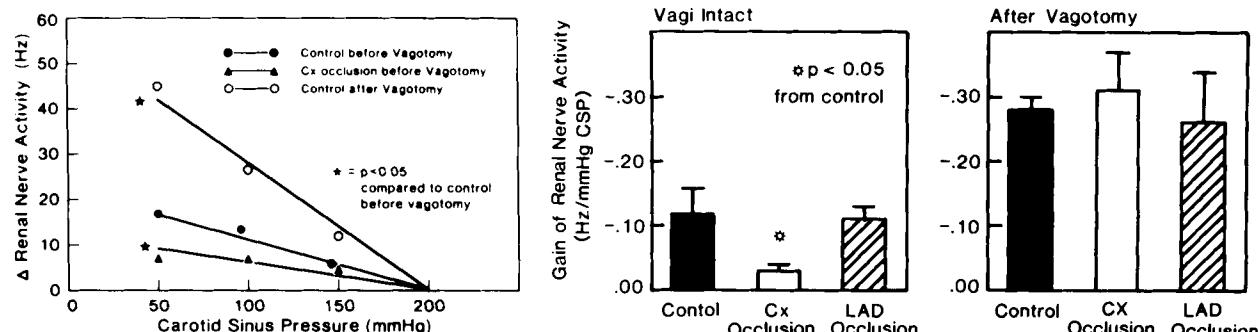


FIG. 35. *Left panel:* interaction between activity of cardiac vagal afferents and carotid baroreflex control of renal nerve activity in anesthetized dogs. Reduction in carotid sinus pressure in dogs with section of the aortic depressor nerves causes significant increases in renal nerve activity. Reflex gain in bar graphs (means \pm SE of renal nerve activity change in Hz per unit change in arterial pressure) declines significantly during occlusion of circumflex (Cx) but not during occlusion of left anterior descending arteries (LAD). After bilateral vagotomy, gain is markedly enhanced and Cx and LAD occlusion have no effect on the gain. [Data from Abboud (6) and Waickman and Abboud (656).]

in left atrial pressure there is less inhibition of renal sympathetic activity and less natriuresis and diuresis (637). Caution should be exercised in interpreting responses to volume expansion in SHR because their decreased venous compliance results in greater increments in left atrial pressure than in the normotensive Wistar-Kyoto rats. This causes greater activation of cardiac afferents despite their higher threshold and results in a paradoxical greater reflex inhibition of sympathetic efferents in SHR than in Wistar-Kyoto rats (529).

Sodium restriction and cardiac afferent activity. In dogs on a restricted sodium intake for a period of 3 wk, the suppression of renal nerve activity is greater when arterial pressure increases but the increase in renal nerve activity is lesser when arterial pressure falls (209). Suppressing reflex increases in renal nerve activity with sodium deprivation is ascribed to increased vagal sensory afferent activity because renal nerve activity is equivalent in the salt-deprived and the control group after a bilateral vagotomy. Despite a decline in total blood volume during sodium restriction, the augmented cardiac afferent activity has been ascribed to a relative increase in central blood volume (209).

Excessive sodium intake and cardiovascular reflexes in hypertension. Increased sodium intake increases sympathetic efferent activity and exaggerates the vasoconstrictor reflex responses in animals or humans with a genetic predisposition for hypertension. Several different mechanisms may mediate these effects.

1. Sodium may decrease norepinephrine turnover in the CNS, inhibit central catecholaminergic pathways, and increase peripheral sympathetic activity. This mechanism may contribute to DOCA-salt hypertension (101).

2. Excessive sodium intake in humans with borderline hypertension causes vasoconstriction and elevates arterial pressure, whereas in normal subjects it causes vasodilatation without a rise in arterial pressure (4, 226, 343, 348, 438, 473). The increased vascular resis-

tance during excessive sodium intake is associated with a significant augmentation of reflex vasoconstrictor responses to LBNP without a significant increase in the vasoconstrictor response to intra-arterial norepinephrine (4, 438). These and other studies in humans by our group and others (4, 226, 275, 343, 438) indicate that excessive salt intake may increase sympathetic activity, and raise vascular resistance and arterial blood pressure in subjects who are salt sensitive or have borderline hypertension. Salt intake may also facilitate the release of the neurotransmitter norepinephrine, and this effect may be more pronounced in borderline-hypertensive subjects (4, 226, 275, 343, 348, 416, 536).

3. In the Dahl salt-sensitive strain of rats, sodium intake increases arterial pressure and exaggerates neurogenic sympathetic vasoconstriction. Takeshita and Mark (604) reported that a high-sodium diet potentiates the vasoconstrictor response to sympathetic stimulation in Dahl salt-sensitive rats but does not augment responses to norepinephrine, suggesting that high salt intake facilitates the release of endogenous norepinephrine from adrenergic terminals, proposed earlier from the work in humans (4, 275, 438).

4. Excessive sodium intake may, through a variety of mechanisms, affect membrane potential and either augment sodium potassium ATPase activity in the baroreceptors, decreasing firing, or inhibit sodium potassium ATPase activity in vascular muscle, possibly through the release of a natriuretic factor, increasing vasoconstrictor responsiveness (259, 488). These effects also would increase neurogenic vasoconstriction. A detailed analysis of all these factors is not possible without much more experimental data.

RENAL AFFERENTS. The kidney is a sensory organ where changes in renal perfusion pressure or chemical stimulation may stimulate neural afferent impulses (520). Electrically stimulating these afferents gives hemodynamic responses analogous to hypothalamic stimulation with vasoconstriction in contralateral renal and mesenteric beds and vasodilatation in the

hindlimb. These afferent nerves affect the discharge rate of single units in the medulla and hypothalamus of the cat (95) and in the anteroventral third ventricle of the rat (352). Increased activity of renal afferents may contribute reflexly to the sympathetic tone in renal hypertension, in DOCA-salt hypertension (337, 338), and in the SHR (676) because renal denervation lowers arterial pressure in these models independently of efferent denervation.

Further work is necessary to determine the importance of this mechanism in the reflex control of arterial pressure.

CONCLUSION

As is evident from the many studies cited in this and other chapters in the *Handbook*, cardiovascular

reflexes play an important role in controlling the circulation in health and disease. The interaction of these reflexes gives rise to integrated responses that depend highly on the state of the organism. Thus, in pathophysiological states such as hypertension, heart failure, and myocardial infarction, alterations in the CNS and in neuroeffector mechanisms may strikingly alter the integrated physiological responses. These responses cannot be predicted from studies of isolated individual reflexes. The integrated responses in an intact organism are rarely the sum of individual responses. The questions of the integrated control of the circulation are difficult and challenging. Answering them will improve our understanding of and ability to treat diseases associated with enormous morbidity, mortality, and socioeconomic impact.

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