The Autonomic Nervous System and Regulation of Cardiovascular Performance

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PROMINENT AMONG the control mechanisms available to the body for the modulation of cardiovascular performance is the autonomic nervous system, the activity of which provides a rapid, sensitive means for the support of the circulation. Thus, for the most part, working in consort with the loading mechanisms for the intrinsic regulation of cardiovascular function and certain local and humoral factors, autonomic influences on the heart and blood vessels regulate the action of the cardiocirculatory system. It is clear from studies in experimental animals that autonomic nerves terminate in all components of the circulation—in the atria and ventricles, as well as in all regional vascular beds; however, the distribution of these nerve endings to the parasympathetic and sympathetic divisions is not uniform. In addition, the functional significance and interactions of this innervation are complex; the contribution of autonomic discharges in the regulation of cardiocirculatory dynamics varies greatly according to physical activity and, even at rest, in the presence of certain disease states. To complicate the picture further, in the sympathetic nervous system, the effector cells, located in approximation with the adrenergic nerve endings, have been separated into two functionally-distinct receptor types. It is recognized that a comprehensive review of a rapidly-changing subject under such intensive investigation as the autonomic control of the cardiovascular system is a difficult undertaking. It is the purpose of this discussion to review certain aspects of our present knowledge, and to integrate the influences of the autonomic nervous system on the separate components of the circulation as they relate to the function of the cardiovascular system as a whole. In addition, some recent findings relating to modifications of autonomic activity in congestive heart failure are considered.

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Parasympathetic and Sympathetic Divisions

When considering the efferent autonomic pathways linking the central nervous system to the cardiovascular system, it is helpful to recall that, for all practical purposes, the parasympathetic nerves, by way of the vagi, carry impulses only to the sinoatrial and atrioventricular nodes and to the atrial myocardium. In contrast, sympathetic innervation is distributed to all areas of the circulation, including the myocardium and specialized conduction structures of both the atria and ventricles and the smooth muscle of the walls of the arterioles and veins. It is now firmly established that nerve impulses are transferred across synapses to end-organ effector sites by the liberation of specific chemical substances, neurotransmitters, which are synthesized, stored, and released from the axon endings.[1] The neurohumoral transmitter of both parasympathetic and sympathetic preganglionic fibers and of parasympathetic postganglionic fibers is acetylcholine, while norepinephrine is the transmitter in virtually all postganglionic sympathetic fibers. Also to be remembered is that the direct control of the circulation may be supplemented by catecholamines released into the blood stream by adrenergic stimulation of the adrenal medulla and, in some instances, by the organs richly endowed with sympathetic fibers.[2] In contrast to sympathetic postganglionic nerve endings, the principal biologically-active substance released by the adrenal medulla is epinephrine.

The traditional concept is that the sympathetic and parasympathetic systems are physi-

ologic antagonists and that the level of autonomic activity in organs innervated by both divisions is the sum of the two opposing influences. In the case of cardiovascular control, this view is generally applicable only to the electrophysiologic properties of the sinoatrial and atrioventricular nodes and the contractile and electrophysiologic characteristics of atrial muscle. Thus, autonomic influences on the inotropic state of the ventricular myocardium and on the degree of constriction of vascular smooth muscle are mediated essentially by alterations in the activity of the sympathetic nervous system.

Alpha- and Beta-adrenergic Receptors

The receptors for the sympathetic nervous system, located at the effector cell of the end organ, have been separated into two types; in the cardiovascular system, activation of the alpha-adrenergic receptors results in arteriolar constriction, while stimulation of the beta component produces positive inotropic and chronotropic effects and dilates arterioles.[3] In the regional circulations, these adrenergic receptors are not partitioned equally, either as to receptor type or as to absolute number of receptors. Thus, the arterioles of the coronary and cerebral beds appear to contain relatively few adrenergic receptors, while the vascular beds in most other areas possess abundant receptors. It is important to note that in the arteriolar bed of skeletal muscle humorally-transported norepinephrine acts on both alpha and beta receptors, while neuronally-released norepinephrine stimulates alpha receptors only.[4] In regard to the capacitance beds, it is generally agreed that they contain both alpha and beta receptors, and that stimulation of the alpha receptors produces venoconstriction; however, the function of the beta system is not settled entirely, although current evidence suggests that activation of these receptors also enhances venous tone.[5]

It is emphasized that the concept of alpha and beta-adrenergic receptors carries only functional meaning and no anatomic or chemical component has been identified for these receptors. The beta-adrenergic receptors are intimately related to the enzyme adenylcyclase, which mediates the intracellular transformation of adenosinetriphosphate to 3',5'-adenosinemonophosphate (cyclic AMP).[6] Present evidence indicates that beta-receptor stimulation results in the accelerated formation of cyclic AMP through action on adenylcyclase, and that cyclic AMP is responsible for the stimulation of myocardial contractility,[7] perhaps by enhancing cell-membrane permeability to calcium ions.[8]

Reflex Control of the Heart and Circulation

The physiologic control of the heart and circulation involves special receptors within the cardiovascular system sensitive to changes in hemodynamics and to alterations in the chemical composition of the blood. These sense organs communicate with the control centers in the central nervous system by impulses discharged through afferent pathways in the glossopharyngeal and vagus nerves. The areas in the central nervous system responsible for the integration of information transmitted from the peripheral receptors and from higher regions in the brain are not completely defined, but it is acknowledged that there are important vasomotor and cardiac control centers in the brain stem which are connected to the autonomic centers in the hypothalamus and sensory areas in the cerebral cortex. Neural discharges from the brain stem centers are transported by pathways to the efferent preganglionic fibers of the vagi in the spinal cord to the sympathetic nerves.

The sensors that receive impulse traffic in the principal afferent pathways for the reflex control of arteriolar tone are situated in the carotid and aortic arch baroreceptors and chemoreceptors, in the stretch receptors in the ventricular chambers, and in the low-pressure areas of the intrathoracic vascular bed.[9] Not only are the nerve endings in the carotid and aortic areas sensitive to alterations in mean blood pressure, but they respond to changes in pulse pressure and the rate at which arterial pressure rises. Following an increase in the distending pressure within the left ventricle, a reflex peripheral vasodilation and bradycardia has been observed in experimental animals.[10] It has been postulated that this reflex mechanism might be of some importance in the pathogenesis of shock due to myocardial infarction; the overdistended ventricle elicits

a reflex which tends to lower peripheral vascular resistance and, in this manner, prevents the increase in systemic vascular resistance from rising to a maximal level.[11] In addition, stretch receptors in the atria and the pulmonary vascular bed appear to initiate arteriolar dilation.[12]

The chemoreceptors present in the carotid aortic bodies, and probably also in the walls of the ventricles, are stimulated by a fall in oxygen tension, a rise in carbon dioxide tension, and a rise in the hydrogen ion concentration of the blood, actions which lead to arteriolar constriction.[13] However, unlike the baroreceptors, the chemoreceptors do not exhibit much activity during ordinary conditions at rest. When interpreting the effects of hypoxia on the circulation, it is important to remember that the action of reflex increase in vascular resistance is partially opposed by the direct effect of lowered oxygen tension to produce arteriolar dilation.[13] Further, the direct myocardial depressant action of hypoxia tends to offset the reflex elevation of myocardial contractile force mediated by the chemoreceptor reflex arc.[13]

Relatively little information is available concerning the location of the afferent limbs of reflexes that are capable of initiating changes in venomotor tone. Present evidence suggests that such receptors exist in the low-pressure vascular compartments within the chest.[14] Observations in experimental animals have demonstrated that stimulation of both the baroreceptors and chemoreceptors reduces the distensibility of the capacitance vessels.[15] Somewhat surprisingly, however, investigations carried out in intact man have not produced evidence to indicate that changes in blood pressure in the physiologic range induce reflex alterations in venous tone.[16] Perhaps it is not unreasonable to anticipate that venoconstriction does occur when reductions in arterial pressure are pronounced. The effects of stimulation of the baroreceptors on venous tone continues to be under active investigation.

Autonomic Control of the Heart

Now that the various components of the afferent and efferent autonomic pathways, the central nervous control areas that modulate this activity, and the peripheral receptors in the cardiovascular system responsive to autonomic output have been considered, it is appropriate to synthesize this information to provide an appreciation of the autonomic mechanisms governing the regulation of the heart and peripheral circulation. The frequency of cardiac contraction above a certain intrinsic rate is determined by the balance between parasympathetic inhibitory influences and sympathetic excitatory actions on the rate of impulses discharged from the pacemaker cells comprising the sinoatrial node. It has long been recognized that there is an inverse relationship between blood pressure and heart rate; when the pressure rises the heart rate declines, a decrease mediated reflexly through the baroreceptor system. In considering the efferent limb of this reflex, the traditional view has been that there is a reciprocal relationship between vagal and adrenergic activity. Recent investigations have shown that this relationship is more complex and is critically dependent on the existing level of basal autonomic activity (fig. 1). Thus, in anesthetized dogs and in supine resting man, when arterial pressure rises the heart rate slows, principally as a result of parasympathetic activation.[17] On the other hand, when background sympathetic activity is elevated in the sitting position

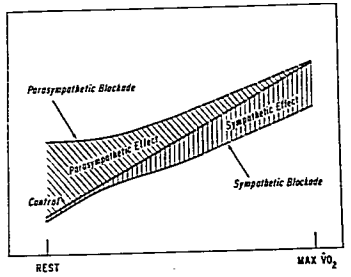

FIG. 1. Schematic diagram showing the relative contributions of the sympathetic and parasympathetic systems to cardioacceleration at various levels of exercise. Broken lines are extrapolations. Comparisons are between control (no blockade) state and parasympathetic or sympathetic blockade with atropine and propranolol respectively. (Reproduced by permission from Robinson, B. F., Epstein, S. E., Beiser, G. D., and Braunwald, E. *Circulation Res.* 19: 400, 1966.)

and especially during upright exercise, significant cardiac slowing consequent to pressure elevation occurs through sympathetic withdrawal.[18]

The contractile state of the ventricular myocardium is influenced profoundly by discharges from the adrenergic nervous system. Thus, beta-adrenergic stimulation, such as that brought about by beta-sympathomimetic drugs, or reflexly consequent to hypotension or to anxiety and painful stimulation as a result of the release of norepinephrine from sympathetic nerve endings, leads to enhancement of the contractile properties of the cardiac chambers. In intact man, this positive inotropism is evidenced by an elevation of the ventricular function curve relating stroke work to the distending pressure of the ventricles, a reduction in cardiac dimensions, and an increased velocity of ejection and enhanced rate of tension development (fig. 2).[19] It is of considerable interest that the administration of beta-adrenergic blocking agents does not lower the basal heart rate or diminish cardiac output and contractility much, findings suggestive that the activity of the sympathetic nerves innervating the heart in resting, supine man exerts only a slight tonic influence (fig. 3).[20, 21] Recent important studies have shown that cardiac adrenergic innervation and catecholamine stores are not necessary for the maintenance of the intrinsic contractile properties of the heart.[22] In this regard, denervation of the heart by surgical means and by catecholamine-depleting drugs does not alter the contractility of intact ventricles or isolated papillary muscles removed from denervated hearts.[23]

There has been a great deal of interest recently in the fact that cholinergic fibers can be demonstrated in the ventricular myocardium. In the intact canine heart, stimulation of the vagi results in a negative inotropic effect on the left ventricle.[24] However, the physiologic significance of parasympathetic innervation of the ventricles has not been determined in regard to the regulation of contractile force.

Autonomic actions on the atria can be shown easily in experimental animals. Sympathetic activation produces a more forceful atrial contraction and thus increases the ventricular end-diastolic fiber length.[25] In contrast to the ventricles, parasympathetic stimulation results in a marked decrease in atrial contraction, thereby reducing ventricular filling and indirectly depressing ventricular per-

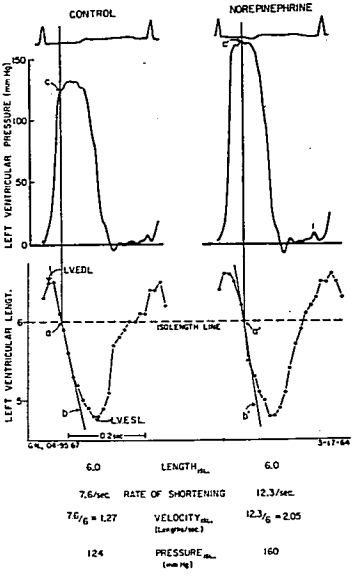

FIG. 2. The instantaneous force–velocity relation on a beat-to-beat basis before and following the administration of norepinephrine to a patient who has undergone operative closure of an atrial septal defect. At the time of corrective operation, small silver-tantalum markers had been sutured to the left ventricle. From above downwards are shown the electrocardiogram, the left ventricular pressure pulse, and the curve relating left ventricular dimensions, determined at 1/30-second intervals, to time. L.V.E.D.L. = left ventricular end-diastolic length; L.V.E.S.L. = left ventricular end-systolic length. On the left are the data obtained during the control period and on the right the observations made during the infusion of norepinephrine. Points a and a' represent the isolength points at which both instantaneous velocity of shortening and intraventricular pressure are determined. Lines b and b' are the tangents to the length curves at points a and a' and represent the velocity of shortening at these points. The steeper slope of b' as compared with b signifies an augmentation of velocity. Points c and c' represent the temporally related points on the ventricular pressure curve. (Reproduced by permission from Glick, G., Sonnenblick, E. H., and Braunwald, E. *J. Clin. Invest.* 44: 978, 1965.)

formance.[25] Further, adrenergic and vagal effects on the electrical properties of heart muscle, particularly on its specialized conduction tissue, can alter cardiac function significantly.

Autonomic Control of the Peripheral Circulation

The extent of constriction of smooth muscle in the walls of arterioles and veins is governed to a major degree by the activity of the sympathetic nervous system. In the modulation of cardiovascular function, the performance of the heart is rendered more effective by certain adjustments in the peripheral vascular beds mediated by adrenergic stimulation. Adrenergic regulation of the peripheral circulation is important when an imbalance exists between the cardiac output and the perfusion requirements of the peripheral tissues; this imbalance may be present at rest, such as in congestive heart failure, and may occur in normal subjects during muscular exercise and in response to other conditions of stress.

In general, regional blood flow is regulated by alterations in vasomotor tone, which in turn is controlled by intrinsic, humoral, and neural influences. The local control of smooth muscle tone of the arterioles is achieved principally by vasodilation produced by metabolic products and hypoxia. The resistance of the arterioles is also regulated by sympathetic vasoconstrictor fibers. Vasoconstriction is produced by augmentation of reflex sympathetic nervous activity, and vasodilation occurs as a result of increased local metabolic vasodilator factors and of decreased sympathetic vasoconstrictor impulses. Although, in skeletal muscle, sympathetic postganglionic fibers which release acetylcholine and produce arteriolar and venous dilation can be demonstrated, the physiologic significance of this innervation is probably minimal.[12, 26, 27]

In terms of the distribution of the cardiac output in the major organs of the body, the largest vascular bed is the splanchnic circulation, which receives approximately 25 per cent of the total cardiac output in fasting sub-

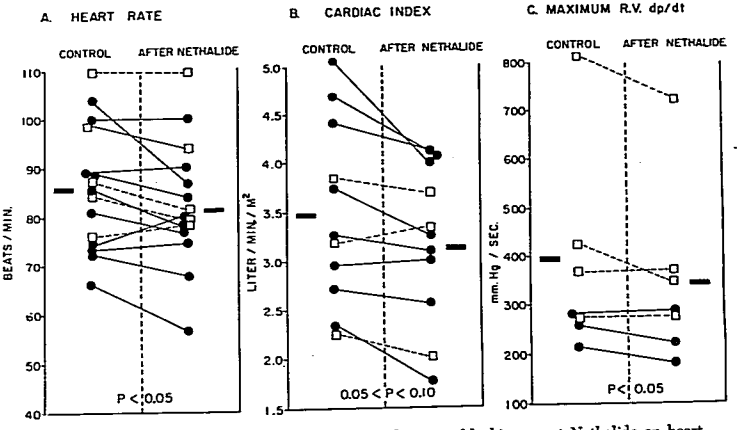

FIG. 3. The effects of 1.5 mg./kg. of the beta-adrenergic blocking agent Nethalide on heart rate, cardiac index, and the maximum rate of pressure increase in the right ventricle (R. V. dp/dt). The solid circles connected by the solid lines represent the observations in patients with idiopathic hypertrophic subaortic stenosis while the open squares connected by the broken lines represent observations in the postoperative patients who had recovered from corrective cardiac operations. The horizontal black bars represent the mean values. (Reproduced by permission from Harrison, D. C., Braunwald, E., Glick, G., Mason, D. T., Chidsey, C. A., and Ross, J., Jr. *Circulation* 29: 94, 1964.)

jects at rest, while the oxygen uptake of this region accounts for a similar fraction of the total oxygen consumption of the body (fig. 4A).[28] This proportionality of oxygen uptake to blood flow is characteristic of the splanchnic circulation; all other organs exhibit a disproportionate relation between oxygen consumption and regional flow. The second largest of the peripheral circulations is the renal circulation, which receives 20 per cent of the cardiac output. Since the oxygen saturation of blood from the renal vein is only slightly less than that of arterial blood, the oxygen consumption of the kidney is small compared to its blood flow. The brain receives about 12 per cent of the cardiac output but consumes a greater proportion of oxygen, 20 per cent. Although the heart is supplied with only 4 per cent of total body flow, it consumes nearly three times this percentage of the oxygen utilized by the body. Skeletal muscle blood flow is approximately 20 per cent of the cardiac output, while these tissues utilize about 30 per cent of the total oxygen uptake of the body. Thus, the musculature consumes a greater share of oxygen than any other organ system in the body and, like the cardiac and cerebral circulations, extracts a large amount of oxygen relative to blood flow. Since the primary function of the cutaneous circulation is the regulation of body temperature, the rate of blood flow to the skin is very labile. However, in terms of percentage for the body as a whole, this regional bed receives a flow which is nearly five times its oxygen consumption. Thus, the low metabolic requirements relative to blood flow of the skin are similar to those of the kidney, and it is these circulations that are constricted reflexly when the cardiac output falls.

In addition to the basic function of the venous system of returning blood to the heart, the capacitance vessels participate actively through reflexes mediated by the sympathetic nervous system in maintaining normal circulatory function, and can constrict in response to physiologic stimuli to preserve venous pressure and to augment venous return. Thus, in response to emotion, cold environment, norepinephrine, hyperventilation, muscular exercise, and the assumption of upright posture, venoconstriction occurs, accompanied by a

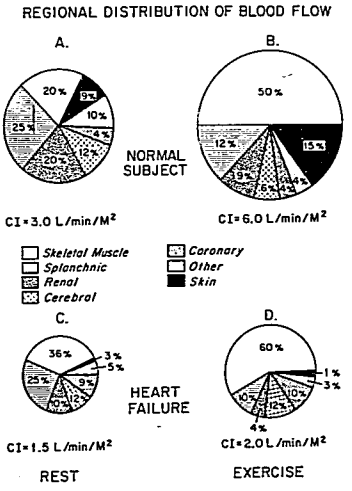

FIG. 4. Regional distribution of blood flow at rest and during exercise in normal subjects and in patients with heart failure. C. I. = cardiac index.

shift of blood in the systemic venous reservoir toward the central circulation.[14] In general, the veins appear to respond to sympathetic and humoral effects less rapidly and quantitatively than do the arterioles.

Autonomic Activity and Muscular Exercise

The control of cardiac function during muscular exercise involves the integration of at least three important factors—heart rate, the contractile state of the heart, and the Frank-Starling mechanism.[29] It is now acknowledged that the sympathetic nervous system mediates, to a large extent, alterations in two of these influences during exercise, the increase in the frequency of contraction and the augmentation of the inotropic properties of the myocardium.[30] In addition, vagal withdrawal contributes to chronotropism, and the effect of the change in heart rate itself improves the fundamental contractile properties of the heart.[30] Thus, leg exercise, performed in the presence of beta-adrenergic receptor

blockade produced by propranolol, is accompanied by a limited elevation of heart rate and contractility, leading to a diminished increment in cardiac output and, during maximal exertion, a reduction in exercise tolerance.[21] Adrenergic stimulation of myocardial contractility and tachycardia *per se* both result in a reduction of ventricular end-diastolic dimensions [20]; a decrease in heart size is also observed during uncontrolled exercise.[20, 21] Thus, at the time of submaximal exercise during beta-adrenergic blockade, endurance may not be diminished, since the operation of the Frank-Starling mechanism is only mildly opposed by tachycardia, and an increase in ventricular end-diastolic dimensions actually occurs.[20] In addition, there is an increase in the amount of oxygen extracted by the peripheral tissues during exercise following the administration of propranolol.[21]

Also contributing importantly in the adaptation of the circulation to the stress of muscular exercise is the action of the sympathetic nervous system on the arterioles and veins. The effect of increased adrenergic activity on the capacitance vessels to augment venous return during exercise has been mentioned. In regard to the resistance vessels, the sympathetic nervous system enhances the effectiveness of the cardiac output enough to satisfy the augmented oxygen demands of the exercising skeletal muscles (fig. 4B). It is now recognized that the augmented blood flow to exercising muscles is accomplished, not only by an increase in the total cardiac output, but also by the redistribution of blood flow brought about by interplay between increased adrenergic activity and local vasodilator influences. With mild to moderate exercise, blood flow to active skeletal muscles rises, accompanied by an elevation of coronary blood flow, while splanchnic and renal flow are reduced.[25] Blood flow to nonexercising skeletal muscles is diminished during moderate to strenuous activity.[32] The cerebral circulation is maintained during moderate activity, but when maximal exercise is performed, there is a tendency for this flow to become slightly reduced as a result of the fall in arterial carbon dioxide tension that accompanies hyperventilation. The circulation in the skin varies with the intensity and duration of exercise.[28, 32] At the onset of exercise, flow declines, but in order to eliminate heat, the cutaneous flow rises as activity continues. However, with maximal exercise, this augmented flow to the skin often is delayed until after the exercise is terminated. Thus, vasodilation occurs in the arteriolar beds of the exercising skeletal muscle and the heart, while vasoconstriction takes place in the gut and kidney, and to a lesser extent in the skin and resting muscle. In considering the mechanisms by which the redistribution of regional flow is accomplished, it is believed that local flow is augmented in response to the accumulation of vasodilator metabolites, and that blood flow to other areas is reduced by reflex arteriolar constriction in order to maintain arterial pressure. This view implies that this reflex sympathetic discharge occurs in all of the regional circulations, but in certain organs this action is overridden by vasodilator influences.

Autonomic Activity in Congestive Heart Failure

When the heart fails as a pump, three major adaptive mechanisms available for the direct support of myocardial function provide a limited amount of cardiac reserve and offset the development of frank congestive heart failure.[33] Thus, the force of contraction can be improved by ventricular dilation through the action of the Frank-Starling principal, by the increase in the number of contractile units by development of ventricular hypertrophy, and by augmentation of the activity of the adrenergic nervous system to enhance cardiac contractility.[34] Recently, a great body of information has been added to our understanding of the role of the sympathetic nervous system in congestive heart failure.[35] Elevated urinary excretion of norepinephrine at rest [36] and increased plasma norepinephrine during exercise [37] have provided evidence of overall augmented adrenergic activity in the body.

Paradoxically, there is a reduction in the concentration and content of the sympathetic neurotransmitter in the failing atrial and ventricular myocardium of experimental animals [34] and man [39] (fig. 5). Current evidence suggests that this diminished quantity of norepinephrine is associated with a total loss of adrenergic nerves from the failing heart; there is no apparent qualitative abnormality in the

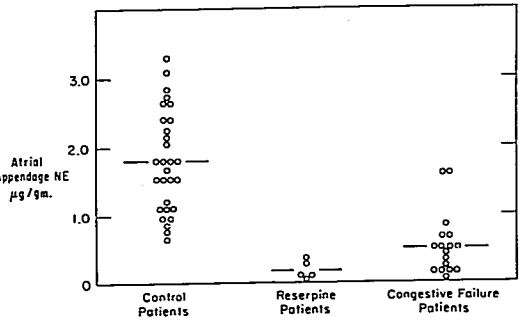

FIG. 5. Concentrations of norepinephrine in the atrial appendages excised at operation in 29 control patients who had not been in congestive heart failure, in five patients who had been treated with reserpine, and in 17 patients who had been in congestive heart failure. (Reproduced by permission from Chidsey, C. A., Braunwald, E., Morrow, A. C., and Mason, D. T. *New Eng. J. Med.* 269: 653, 1963.)

metabolic processes involving norepinephrine in those nerve endings remaining intact.[40] Very recently, reduced activity of tyrosine hydroxylase, the enzyme rate-limited factor in the biosynthesis of norepinephrine, has been demonstrated in the failing myocardium in experimental animals.[41] Although this finding provides an explanation for the reduced myocardial norepinephrine in heart failure, the diminished enzymic activity appears to be related to the total loss of adrenergic nerves from the heart rather than to a qualitative abnormality in biosynthesis. This reduced myocardial norepinephrine has important functional consequences, as shown by the fact that stimulation of the sympathetic nerves to the heart in experimental animals produces abnormally small increments in heart rate and myocardial contractile force.[42] In keeping with the generalized increase in sympathetic activity in heart failure, it appears possible that the activity of the nerves that are intact in the heart might be augmented. Present evidence indicates that the presence of myocardial norepinephrine is not necessary for the full maintenance of the normal intrinsic contractile state of the heart.[22] Therefore, the paucity of myocardial neurotransmitter is thought not to be causally related to the initial biochemical defect responsible for cardiac failure; however, defective sympathetic activity in the heart does represent an important encroachment on a fundamental reserve mechanism for the compensation of heart failure.[40]

It is clear that a state of arteriolar and venous constriction is a characteristic of human congestive heart failure (fig. 6).[35] This vasoconstriction, modulated for the most part by increased sympathetic activity, complements the reduced performance of the heart in the support of circulatory function. The increase in total peripheral vascular resistance in heart failure is an important compensatory mechanism by which arterial pressure is maintained in the face of a low cardiac output. Since the capacitance bed is relatively indistensible in heart failure, venous return is enhanced and cardiac output tends to be maintained.

In addition to the crucial role of the generalized increase in adrenergic activity in the arterioles and veins to sustain adequate arterial blood pressure, heightened sympathetic influences on the regional circulation are largely responsible for the redistribution of total blood flow to the body. Thus, accompanying the fall in cardiac output, there is a decrease in blood flow to most regions of the body. However, since a uniform reduction of flow to all areas might result in a critical decline of tissue oxygen tension in some organs, in severe heart failure this reduction of flow is not uniform and redistribution of flow occurs (fig. 4C).[25] In advanced heart failure, the rate of blood flow to the renal and cutaneous circulations is reduced disproportionately to that of other areas. At the same time, coronary blood flow remains normal at all stages of heart failure unassociated with coronary atherosclerosis, and blood flow to the brain and skeletal muscle tends to be preserved except with advanced heart failure. The blood flow to the splanchnic circulation is reduced in proportion to the

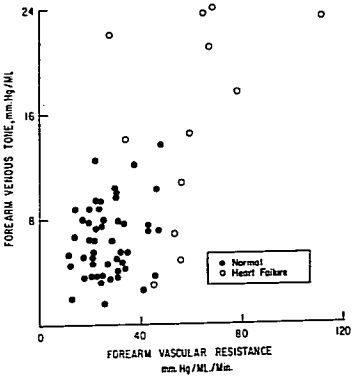

FIG. 6. Relation between forearm venous tone and forearm vascular resistance in normal subjects and in patients with congestive heart failure. (Reproduced by permission from Braunwald, E., Chidsey, C. A., Pool, P. E., Sonnenblick, E. H., Ross, J., Jr., Mason, D. T., Spann, J. F., and Covell, J. W. *Ann. Int. Med.* 64: 904, 1966.)

fall in cardiac output. It is suggested that adrenergic-mediated vasoconstriction occurs in the kidneys and skin, and thus blood is diverted to the heart, brain and skeletal muscle, which have high metabolic requirements relative to flow. As a consequence of these regional adjudgments in heart failure, there is deterioration of renal function and impairment of the dissipation of heat generated by the metabolic processes within the body.

In patients with heart failure, the cardiac output is relatively fixed during exercise, and fails to respond normally to the increased oxygen requirements of the metabolizing tissues. Certain adjustments, therefore, are necessary in the peripheral vascular beds in order to supply more blood flow to exercising muscle (fig. 4*D*).[28] Present evidence suggests that exercise leads to a less-than-normal augmentation of total flow to the exercising limbs, but that the flow to skeletal muscle in these areas is increased to a normal extent at the expense of flow to the skin. At the same time, the blood flow to the splanchnic and renal circulations and to resting skeletal muscle is reduced.[32] Coronary blood flow is elevated while cerebral blood flow remains unchanged. In this manner, blood flow is directed from the resting areas of the body to the exercising parts. Thus, vasodilation occurs in exercising skeletal and cardiac muscles, and sympathetic-induced vasoconstriction takes place in the gut, kidney, skin, and resting muscles where blood flow declines. This redistribution occurs earlier and to a greater extent than that observed in normal subjects performing similar levels of exercise, although these adjustments during mild to moderate exercise in patients who have heart failure probably are comparable to those in normal subjects during strenuous exertion.[32] In addition to these changes in the resistance vessels, it has been shown that exercise during heart failure leads to an excessive rise in venous tone and central venous pressure mediated by increased sympathetic activity.[43]

Since it is apparent that there is an augmentation of adrenergic activity in the body in heart failure, despite the findings of diminished neurotransmitter in the myocardium, it would appear reasonable to postulate that the elevated plasma and urinary norepinephrine levels reflect increased sympathetic influences in the peripheral vascular beds. This view is consonant with the generalized vasoconstriction, tachycardia, diaphoresis, and oliguria which are characteristic findings in this condition. Also consistent with the suggestion that this increased sympathetic activity is derived from action in the peripheral circulation is the current evidence which indicates there may not be a substantial adrenal medullary component to this sympathetic discharge.[36] In fact, very recent observations suggest the presence of increased labile stores of norepinephrine in the vascular beds of skeletal muscle in patients who have heart failure.[44]

Conclusion: Integration of Autonomic Responses in Circulatory Control

In the foregoing discussion, the concept was developed that the autonomic nervous system exerts specific influences on each of the components of the cardiovascular system, and that these influences are quantitatively most important when there is an unfavorable relation between oxygen needs and availability in the peripheral tissues. Stimulation of the sympathetic nervous system results in a generalized

adrenergic discharge, rather than selective augmentation of nervous activity to separate organs.

For example, a decrease in blood pressure, sensed by the baroreceptors, produces a decline in afferent impulse traffic to central nervous vasomotor centers, which results finally in increased sympathetic activity to the heart and peripheral vasculature. In this manner, several effector mechanisms are stimulated, and simultaneously there is an increase in heart rate, augmentation of cardiac contractility, and arteriolar constriction. In addition, these sympathetic actions on the entire circulation are complemented by withdrawal of parasympathetic influences on cardiac pacemaker activity.

In the control of cardiac output, these cardiac and extracardiac vascular factors are integrated by reflex mechanisms in order to sustain an adequate total blood flow in accordance with the oxygen requirements of the body. Thus, sympathetic stimulation in response to hypotension results in an increase in cardiac output, due to reflex-mediated augmentation of cardiac contractility in the presence of diminished resistance to ventricular ejection. As blood pressure rises consequent to the rise in cardiac output and reflexly-produced arteriolar constriction, sympathetic stimulation is reflexly withdrawn and vagal activity returns, resulting in the stabilization of cardiac output at normal levels.

In regard to the maintenance of regional blood flow in tissues with high metabolic requirements, a sufficient supply of oxygen is assured by the predominant effect of vasodilator metabolites in these critical areas, combined with arteriolar constriction in most of the other vascular beds of the body. By these actions, regional blood flow is redistributed selectively from organs with low oxygen demands to those with elevated requirements.

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