Studies on the Function of the Adrenergic Nerve Endings in the Heart

By Eugene Braunwald, M.D., Charles A. Chidsey, M.D., Donald C. Harrison, M.D., Thomas E. Gaffney, M.D., and Richard L. Kahler, M.D.

It is now clear from a number of studies in experimental animals that the force of myocardial contraction can be profoundly augmented by an increase in the sympathetic influences acting upon the heart. The effects on the myocardium of stimulating the cardiac sympathetic nerves closely resemble those resulting from the injection of the adrenergic neurotransmitter, norepinephrine, and it has been suggested that the cardiac sympathetic nerves play a fundamental role in regulating the activity of the heart. Accordingly, considerable effort is now being directed toward increasing our understanding of the detailed function of the sympathetic nerve endings in the heart and in other organs.

Source and Disposition of Cardiac Norepinephrine

A logical area to begin an investigation of the cardiac sympathetics is to determine the source of the norepinephrine at the nerve endings. It is clear that the heart, among other organs innervated by sympathetic nerves, can extract norepinephrine from the blood stream, and this finding led to the speculation that the heart’s norepinephrine stores are derived from the blood. An intriguing possibility is that the norepinephrine is actually synthesized by the cardiac sympathetic nerve endings. In 1939, a pathway for biosynthesis of norepinephrine through dopamine was suggested (fig. 1) and by means of radioisotopic technics this pathway was confirmed in studies on the isolated adrenal medulla and on sympathetic nerves. It seemed of importance to determine whether or not the heart is capable of synthesizing norepinephrine from its immediate precursor, dopamine. Accordingly, radioactive dopamine was injected into the blood perfusing an isolated canine heart preparation. Analysis of the norepinephrine obtained from the heart one hour later demonstrated that a fraction of it was radioactive; between 1.4 per cent and 12.8 per cent of the norepinephrine present had been formed from the administered dopamine. The formation of norepinephrine was found to be substantially higher in the ventricles than in the atria. Although the rates of formation observed are sufficient to account for a rapid replacement of norepinephrine in the heart, the relative importance of biosynthesis and of extraction of norepinephrine from the blood stream in the maintenance of myocardial norepinephrine stores remains to be elucidated. Recently, other investigators have recovered radioactive norepinephrine from isolated guinea pig hearts which had received radioactive tyrosine.

Four possible fates for the norepinephrine exist following its release from its intracellular storage sites as a result of nerve impulses or humoral stimuli (fig. 2): 1) the adrenergic neurotransmitter may attach to the receptor site of an effector organ, such as the heart, producing an adrenergic response; 2) it may undergo enzymatic degradation; 3) it may return to the store whence it came; or 4) it may overflow into the blood.

Prior to any detailed examination of the second possibility, enzymatic degradation, it should be recalled that norepinephrine is metabolized almost completely prior to its excretion in the urine. The demonstration that 3-methoxy-4-hydroxymandelic acid is a
Figure 1

Route of synthesis and metabolism of norepinephrine.

major metabolic product of norepinephrine\textsuperscript{17} (fig. 1) indicated that two steps are involved in the metabolism of this amine, O-methylation and deamination. Since the enzymes responsible for both O-methylation and deamination, i.e., catechol-O-methyl transferase and monoamine oxidase, are present in the heart,\textsuperscript{18,19} a significant fraction of the released norepinephrine may undergo metabolism before entering the circulation. Although O-methylation is the predominant route of inactivation of intravenously injected catecholamine, the metabolic fate of norepinephrine released from the nerve endings may differ from that of the injected amine, since in the latter instance the role of hepatic metabolism will predominate. It may be questioned whether the relative activities of the two enzymes are the same in the sympathetic nerve endings and in the liver. The manner in which the heart metabolizes norepinephrine was therefore investigated in an isolated canine heart preparation, in which the myocardial norepinephrine pool had been labeled by injecting tritiated norepinephrine into the perfusing blood.\textsuperscript{20} During the first hour following this injection, as the isotopic material, which had been extracted by the heart, was released spontaneously from the norepinephrine pool, more than three fourths was metabolized before appearing in the coronary venous blood. The chief metabolite was found
Distribution of Norepinephrine

With this brief background of information regarding the source and disposition of cardiac norepinephrine, it is pertinent to inquire into the question of the distribution of the cardiac norepinephrine pool. Trendelenburg has suggested that it could be divided into two compartments, a “bound” and an “available” form of norepinephrine.22 This problem was approached in this laboratory by studying the degree of mixing of exogenously administered norepinephrine within the heart. It is now well known that following its intravenous administration, radioactive norepinephrine is preferentially concentrated in tissues innervated by sympathetic nerves, where it is specifically stored in the nerve endings.23 Tritiated norepinephrine was therefore administered to anesthetized dogs and the specific activity, i.e., the ratio of radioactive to nonradioactive norepinephrine, in coronary sinus blood was compared with the specific activity in the myocardium.24 For a period of five hours after the label had been introduced the norepinephrine which was released spontaneously had a greater specific activity than the norepinephrine which was in the myocardium. When norepinephrine release was augmented by tyramine administration or sympathetic nerve stimulation, the specific activity of the norepinephrine in the coronary sinus outflow fell markedly, indicating that these stimuli now released greater proportions of norepinephrine with which the radioactive tracer had not mixed (fig. 3).

In experiments performed 24 and 48 hours after labeling of the pool, the specific activity of norepinephrine in the heart was identical with that in the coronary sinus blood, and when release was augmented the specific activity in the coronary sinus blood did not change. These findings indicate that exogenous norepinephrine initially mixes with that portion of the myocardial norepinephrine store which is in rapid exchange with the blood, and that this portion is small in relation to the entire pool (fig. 3). Therefore, the

Figure 2

Diagrammatic representation of the four possible fates of norepinephrine (NE) upon its release from the intracellular storage sites. MAO = monoamine oxidase, COMT = catechol-O-methyltransferase.

to be normetanephrine, and it was therefore concluded that catechol-O-methyl transferase is the enzyme primarily responsible for the metabolic inactivation of norepinephrine in the canine heart. When release of norepinephrine was increased by the injection of tyramine, a greater quantity of the released norepinephrine appeared unchanged in coronary venous blood. This observation suggests that the enzymatic processes by which norepinephrine is inactivated may be limited. Therefore, the extent to which the local metabolism of norepinephrine contributes to the termination of adrenergic activity in the heart, particularly when this activity is increased in intensity, must still be determined. There is some evidence which suggests that the specific manner in which norepinephrine is metabolized depends upon the specific stimulus for its release. Thus, Kopin and Gordon21 have shown that norepinephrine released by tyramine is metabolized primarily by catechol-O-methyl transferase, while norepinephrine released by reserpine serves as a substrate for deamination by monamine oxidase.
neurotransmitter pool in the heart may be considered to be nonhomogeneous.\textsuperscript{24}

In order to examine the distribution of myocardial norepinephrine from another point of view, a large dose of tyramine was infused continuously for one hour into a group of dogs until the adrenergic response to this agent had been completely abolished. Measurement of the myocardial norepinephrine content at this time revealed that it had been reduced by only 40 per cent.\textsuperscript{25} Thus it may be useful to think of the myocardial norepinephrine stores as being divided into two compartments; the norepinephrine is readily releasable by tyramine from one compartment, but is resistant to the release by tyramine from the other. Axelrod and associates\textsuperscript{26} have reached similar conclusions from their studies with tyramine in an isolated perfused rat heart.

It was then considered of importance to determine whether the norepinephrine store which is available for release by tyramine was identical with that which is available for release by nerve stimulation. Accordingly, the effects of nerve stimulation were examined both before and after tyramine tachyphylaxis had been produced.\textsuperscript{27} It was observed that nerve stimulation following tyramine resulted in a normal adrenergic response, i.e., the augmentations of myocardial contractile force, heart rate, and aortic pressure were essentially identical with those which were observed prior to tyramine (fig. 4). Since nerve stimulation was evidently capable of releasing norepinephrine, when the myocardial store of norepinephrine available to release by tyramine had been depleted, it is clear that some of the "available" norepinephrine can be released by nerve stimulation but not by tyramine (fig. 5). Thus, in addition to the concept that the norepinephrine in sympathetic nerve endings may exist in "bound" and "available" compartments,\textsuperscript{22} it must be considered that the norepinephrine available for release is further subdivided functionally. This subdivision may result either from heterogeneity of the readily releasable norepinephrine or conceivably from the saturation of an intermediate step in the release of norepinephrine by tyramine.

**Mechanism of Action of Drugs**

A number of vasoactive amines resemble tyramine in their ability to release norepinephrine from sympathetic nerve endings.\textsuperscript{25} In this connection, it is of interest to consider the mechanism of action of three drugs, metaraminol (Aramine), guanethidine (Ismelin), and reserpine (Serpasil). These drugs act upon the adrenergic nervous system, they are widely used in clinical practice, and their mechanism of action has recently been investigated intensively.\textsuperscript{28-33}
Metaraminol

The responses of arterial pressure and of myocardial contractile force to graded doses of metaraminol were compared in control dogs, and in animals which had been depleted of their catecholamine stores by the prior administration of reserpine. The circulatory responses to metaraminol were reduced, but were not abolished completely in the latter group of animals. Infusions of norepinephrine to the reserpinized animals restored the responses to metaraminol towards normal. In other experiments, the administration of metaraminol was found to release norepinephrine from the heart into the coronary sinus blood. Two-hour infusions of metaraminol resulted in a reduction of atrial norepinephrine content to approximately half of the control levels (fig. 6) and markedly reduced the hemodynamic responses to single injections of tyramine and metaraminol. It was concluded that a major action of metaraminol results from the release of norepinephrine and that prolonged administration of the drug results in reduction of tissue norepinephrine stores. It is likely, however, that metaraminol also has a direct effect on the myocardium.

These observations are relevant to a relatively common clinical finding, i.e., the progressive diminution in response to metaraminol. Prolonged infusions of metaraminol may reduce the norepinephrine stores in the sympathetic nerve endings in the heart and blood.

Circulation, Volume XXVIII, November 1963
vessels, thereby resulting in a diminution of sensitivity to subsequently administered metaraminol. Under such circumstances, it would seem appropriate to discontinue metaraminol and administer norepinephrine instead. Following repletion of the norepinephrine stores sensitivity to metaraminol may redevelop.

Guanethidine

During the past three years, this drug has become an important agent in the treatment of hypertension, and it is clinically useful because it produces selective postganglionic adrenergic blockade. When administered intravenously to experimental animals and to patients, however, it results in a pressor response, accompanied by marked positive inotropic and chronotropic effects. It was suggested that this initial sympathetic stimulation produced by guanethidine was related to sudden release of norepinephrine from sympathetic nerve endings. In order to test this hypothesis, blood was collected from the coronary sinus following the injection of guanethidine, and relatively large quantities of norepinephrine were found to have been released during the course of the pressor phase. Moreover, the acute effects of guanethidine on the circulation were compared in a group of normal anesthetized dogs, and in a group of dogs which had been subjected to chronic cardiac denervation resulting in total depletion of myocardial catecholamines. It was observed that the increases in arterial pressure, cardiac output, myocardial contractile force, and heart rate were almost totally absent in the cardiac denervated dogs. From these studies it was concluded that sudden release of myocardial catecholamines is largely responsible for the acute circulatory effects of guanethidine.

In view of these findings, and the well known fact that guanethidine is capable of lowering the norepinephrine content of a variety of tissues, it was thought that the
release of norepinephrine from sympathetic nerve endings was responsible for the depletion of norepinephrine stores, and that this depletion of the neurotransmitter is primarily responsible for the adrenergic blockade.

To test this hypothesis, following the intravenous administration of guanethidine, the release of norepinephrine from the heart was determined by measuring the plasma norepinephrine concentration in blood withdrawn simultaneously from the dogs' coronary sinus and femoral artery. The release of norepinephrine into the coronary sinus blood was terminated 2 to 3 hours following the administration of guanethidine. The norepinephrine content of atrial appendage was reduced to only three fourths of control levels 4 hours after guanethidine, whereas total depletion had occurred at 24 hours after the drug had been given. Thus, the reduction of the tissue concentration of norepinephrine continued after measurable release of norepinephrine into the coronary sinus blood had ceased.

In other experiments the responses of the heart rate to cardioaccelerator nerve stimulation were correlated with the myocardial norepinephrine concentrations at various time intervals following the intravenous injection of guanethidine. The chronotropic response to cardioaccelerator nerve stimulation was blocked by guanethidine before a measurable reduction of atrial catecholamine content had occurred; this blockade was not overcome by a prolonged infusion of a relatively large dose of norepinephrine. Hence, the interference with peripheral adrenergic transmission which followed the injection of guanethidine does not appear to be dependent upon depletion of the adrenergic transmitter store. These experiments did not, however, exclude the possibility that the reduction of tissue norepinephrine content is involved in the clinical effects of guanethidine.

**Reserpine**

When administered in large doses to experimental animals, the rauwolfia alkaloids also deplete the tissue stores of catecholamines and serotonin. In order to determine whether this amine-depleting action of reserpine results from, or is related to, the release of tissue norepinephrine stores, coronary arteriovenous differences of norepinephrine were measured and related to the norepinephrine concentration of the myocardium. During the first four hours after the injection of reserpine the tissue stores decreased to one third of the control levels. During this time, however, norepinephrine as the free amine was not released into the coronary venous blood. It is possible that the norepinephrine released by reserpine was metabolized within the sympathetic nerves, as suggested by Kopin and Gordon.

An attempt was then made to establish a quantitative relationship between the size of the neurotransmitter store, as reflected by the myocardial content of norepinephrine, and the degree of adrenergic nerve blockade produced by reserpine. It was observed that the positive chronotropic response to cardioaccelerator nerve stimulation was reduced only after myocardial norepinephrine levels had been reduced by reserpine from control levels of 2.5 to 3.0 μg./Gm. to approximately 0.3 μg./Gm. Thus, these findings suggest that the reserpine-induced blockade of adrenergic transmission may ultimately be dependent upon the depletion of adrenergic transmitter, but that almost complete depletion of stored adrenergic transmitter must occur before reserpine-induced adrenergic blockade takes place.

Two fundamental differences between guanethidine and reserpine, the two antiadrenergic drugs most commonly employed clinically, were thus revealed by these experiments. Guanethidine always released free norepinephrine into the coronary sinus blood, while reserpine did not usually exhibit this action. The adrenergic-blocking activity of guanethidine was not dependent on the tissue stores of norepinephrine, while marked lowering of myocardial catecholamines was required before reserpine blocked the transmission of sympathetic nerve impulses.

*Circulation, Volume XXVIII, November 1963*
In spite of these important differences between the mechanisms of action of the two drugs, an important property which is shared by guanethidine and reserpine was recently demonstrated. By means of the major vessel occlusion technic described by Bartelstone for the demonstration of reflex venoconstriction, it was shown in experimental animals that the administration of either reserpine or guanethidine blocked the reflex venoconstriction secondary to carotid occlusion and central vagal stimulation. It was of interest that guanethidine acted almost immediately, i.e., within 5 minutes after injection. Reserpine, however, required about 1 1/2 hours to block reflex venoconstriction. These findings suggest that in the case of guanethidine the effect was independent of norepinephrine stores, but that catecholamine depletion at the sympathetic nerve endings had to take place before reserpine blocked reflex venoconstriction. These observations on the effects of reserpine and of guanethidine on the venous bed have recently been extended to man. The oral administration of doses of these drugs which are commonly employed in clinical practice blocked the venous constriction that occurred in the forearm during leg exercise or during immersion of the opposite hand into ice water.

The Adrenergic Nervous System in Circulatory Regulation

It is now quite clear that the force of contraction of the heart of experimental animals and of patients can be stimulated profoundly by increasing the number of impulses traversing the sympathetic nerves. It cannot be concluded from such observations, however, that the ordinary activity of the adrenergic nervous system actually has a significant effect on myocardial function in intact human subjects. It was of particular interest to determine whether this system plays a compensatory role in maintaining ventricular contractility when the function of the myocardium is depressed in patients with heart disease, or when the hemodynamic burden placed on the normal heart is increased.

Congestive Heart Failure

The availability of drugs such as guanethidine which selectively block the activity of the adrenergic nervous system has made it possible to estimate the role of this system in the maintenance of myocardial function in man. The effects of the administration of guanethidine to patients with reduced cardiovascular reserve were first determined. In addition to the theoretical interest of such studies, the widespread clinical use of adrenergic blocking drugs in patients with heart disease makes an evaluation of the effects of these drugs on myocardial function of immediate and practical importance. Ten adult patients with inactive rheumatic valvular or primary myocardial disease were studied. Each patient had signs or symptoms of right- or left-sided congestive heart failure at the time of the investigation. The administration of guanethidine increased the clinical manifestations of heart failure in each of five patients who were in functional classes III or IV. In these patients guanethidine resulted in an increase of dyspnea and orthopnea, a decrease in urinary sodium excretion, and an elevation of venous pressure and weight. The administration of guanethidine to the other five patients, who were in functional classes II or III, did not result in any worsening of the congestive heart failure.

It is evident from these studies that interference with the activity of the adrenergic nervous system is capable of aggravating congestive heart failure in some patients with cardiac decompensation. This effect occurred despite the fact that the adrenergic nerve blockade was almost certainly incomplete. These observations therefore suggest that the adrenergic nervous system plays an important compensatory role in the circulatory adjustments of patients to congestive heart failure and they emphasize the need for caution in the use of antiadrenergic drugs, such as reserpine and guanethidine, in the treatment of patients with limited cardiac reserve.
The manner in which the cardiovascular system responds to the increased metabolic demands of muscular exercise has been of considerable interest and it has been suggested that the sympathetic nervous system has an important role in mediating this response in normal man. The normal increase of cardiac output during exercise is attenuated, or even abolished in patients in whom the cardiac reserve is diminished. It was therefore of interest to assess the activity of the sympathetic nervous system in patients with heart disease during the stress of muscular exercise and to compare it with the activity in normal subjects. An index of the activity of the sympathetic nervous system at rest and during exercise was obtained by measuring the concentration of norepinephrine in arterial blood, a method which had previously been employed for this purpose by other investigators.\textsuperscript{40} In normal individuals very small increases in the arterial norepinephrine concentrations were noted during exercise.\textsuperscript{40, 41} Although the levels of exercise were comparable, the augmentations of plasma norepinephrine induced by exercise in patients with congestive heart failure exceeded those observed in the normal subjects (fig. 7). This excessive elevation of arterial norepinephrine concentration is interpreted to reflect an increased activity of the sympathetic nervous system. Since, as already noted, increased activity of the sympathetic nervous system augments myocardial contractility, it is possible that the heightened sympathetic activity observed during exercise in patients with heart failure plays an important role in supporting their myocardial function.

**Exercise**

An attempt was then made to clarify the role played by the autonomic nervous system in mediating the circulatory response to exercise in normal human subjects by determining the effects of inhibition of the parasympathetic and the sympathetic divisions.\textsuperscript{42} The investigations were carried out on a group of healthy male subjects, studied in the supine position. Measurements of heart rate, cardiac output, arterial blood pressure, and oxygen consumption were made at rest and during exercise. The control study was performed without prior drug administration. Oral guanethidine was then begun and the dose was progressively increased every other day for a period of 21 to 25 days. The maximum daily dose of guanethidine ranged from 50 to 85 mg, while atropine was given intravenously in a dose of 2 mg. Exercise consisted of pedaling a bicycle ergometer at a constant rate. The effects of exercise were determined after guanethidine administration and then under the influence of both atropine and guanethidine. Cardiac output was measured by the indicator-dilution technic with indocyamine dye, which was injected into the right atrium.

The exercise was identical during the control period and after the administration of guanethidine and atropine. This was reflected in the finding that the increase in total body

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**Figure 7**

A comparison of the response of the arterial plasma norepinephrine concentration to exercise in normal subjects and in patients with congestive heart failure (CHF). The intensity of exercise is expressed in multiples of the control, resting oxygen consumption (C). The stippled area represents the range encountered in normal subjects. The circles represent the values encountered in individual patients with congestive heart failure, with the circles on the left signifying the levels of arterial norepinephrine at rest, and the circles on the right indicating the levels during exercise.
oxygen consumption associated with the exercise was identical under both conditions. It was observed that pharmacologic inhibition of the autonomic nervous system markedly reduced the magnitude of the circulatory response to exercise. During the control study, a level of exercise which resulted in a four- to five-fold increase in oxygen consumption, produced average increases above resting values of 68 per cent in heart rate, 17 per cent in the stroke volume index, 96 per cent in the cardiac index, and 129 per cent in the left ventricular minute work. After the administration of atropine and guanethidine, identical levels of exercise resulted in average increases above resting values of only 28 per cent in the heart rate, 1 per cent in the stroke volume, 30 per cent in the cardiac index, and 5 per cent in left ventricular minute work. The absolute values of cardiac index, systemic arterial pressure, ventricular work per minute and per beat were significantly lower and the values of the arteriovenous oxygen differences were significantly higher during exercise following atropine and guanethidine than during the control study.

Blockade of the parasympathetic nervous system alone elevated the heart rate, cardiac index, and left ventricular minute work at rest and did not interfere with the circulatory response to exercise. Guanethidine alone slowed the resting heart rate, but did not affect cardiac output or arterial pressure at rest. The cardiac index, mean arterial pressure, and left ventricular work during exercise were lower after guanethidine than during the control study. These studies demonstrate the important contribution made by the autonomic nervous system to the circulatory response to exercise in man and indicate that the sympathetic division plays the major role in this regard.

From these investigations the following tentative hypothesis regarding the role of the autonomic nervous system in circulatory regulation might be suggested. The adrenergic nervous system increases its stimulation of the myocardium at a time when an imbalance, or a potential imbalance, exists between the cardiac output and the perfusion requirements of the peripheral tissues. Such an imbalance may occur in the patient with congestive heart failure at rest, in whom withdrawal of sympathetic stimulation by guanethidine may result in an intensification of heart failure.39 However, the withdrawal or reduction of sympathetic impulses does not induce cardiac decompensation in normal individuals, or in patients with heart disease who are not suffering from congestive heart failure. One possible explanation for this finding is that the sympathetic nervous system contributes little to the maintenance of cardiac activity in such individuals when they are at rest. An alternate possible explanation is that in the absence of cardiac failure an augmentation of the force of cardiac contraction through the operation of the Frank-Starling mechanism can still take place in spite of any depression of myocardial function evoked by the withdrawal of sympathetic impulses.

During the stress of muscular exercise the function of the adrenergic nervous system assumes greater importance. In patients with congestive heart failure the intense activity of this system is reflected in the extremely high levels of circulating catecholamines which may occur under these conditions.41 Even in normal subjects, however, the autonomic nervous system plays a significant role in stimulating the myocardium during muscular exercise. This increased activity is reflected by the augmentation of the urinary excretion of norepinephrine43 and the tendency for the circulating norepinephrine concentration to increase slightly.40,41 Inhibition of the adrenergic nervous system alone prevents the increase in stroke volume which normally occurs during exercise. Adrenergic blockade, however, still permits an increase in cardiac output to occur as a result of a marked increase in heart rate, presumably mediated through the withdrawal of vagal impulses. When the parasympathetic nervous system is blocked in addition to the sympathetic, the circulatory response to exercise is further reduced, and the mixed arteriovenous
oxygen difference during exercise rises significantly above the levels encountered in the individuals in whom the autonomic nervous system is intact.\textsuperscript{42}

Conclusions

Although it has been established for many years that the activity of the heart can be influenced profoundly by changes in activity of the autonomic nervous system, recent advances in biochemical technique have made it possible to study the sources and disposition of the adrenergic neurotransmitter in cardiac tissues. Evidence was presented for the ability of the isolated heart to synthesize norepinephrine and for the importance of the enzyme, O-methyl transferase, in the inactivation of norepinephrine by the heart. In addition, the experimental data supporting the concept that the norepinephrine at the sympathetic nerve ending is not in a homogeneous store, but that it is partitioned into several pools or functional compartments, were reviewed. It is likely that further elucidation of this partitioning of norepinephrine in the sympathetic nerve endings will contribute to an understanding of the mechanism of action of drugs which act upon the sympathetic nervous system.

Experimental data which showed that metaraminol acts on the circulation primarily by releasing norepinephrine were reviewed. The mechanisms of action of guanethidine and reserpine were contrasted; the ability of guanethidine to block the adrenergic neuro-effector junction is not dependent on the depletion of tissue norepinephrine stores, while these stores have to be lowered markedly in order for reserpine to block the effects of stimulating sympathetic nerves. Guanethidine releases free norepinephrine into the coronary venous blood, but its norepinephrine-depleting action is not dependent on this property. Reserpine, on the other hand, lowers tissue norepinephrine stores more rapidly than does guanethidine, but does not release norepinephrine, as the free amine, into the circulation.

The importance of the sympathetic nervous system in circulatory regulation during muscular exercise and in the presence of impaired myocardial function was demonstrated. Evidence was reviewed for the concept that the activity of the adrenergic nervous system is of particular importance to the maintenance of circulatory adequacy when an imbalance develops between the cardiac output and the perfusion requirements of the peripheral tissues.

References

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