The Sympathetic Nervous System, the Vascular Volume and the Venous Return in Relation to Cardiovascular Integration

The effect of the sympathetic nervous system on the circulation has long been a subject for investigation. In the past, most emphasis was placed on the role of this system in the regulation of arteriolar tone. This is its most obvious effect but recent studies have also emphasized the importance of the sympathetic system in adjusting the total vascular volume and, hence, venous return and cardiac output. In these experiments norepinephrine, which mimics sympathetic vasoconstriction, and hexamethonium, which produces sympathetic inhibition, were employed as pharmacologic tools.

The pertinent experiments were as follows: A pump, with output which remained constant under marked variations in peripheral resistance, was substituted for the left ventricle in a dog. The pulmonary drainage of blood was carried to a reservoir by means of a plastic tube inserted into the left auricle. The blood was pumped from the reservoir through a T-tube in the descending thoracic aorta. The right ventricle was left undisturbed. This preparation maintained normal intravascular pressures with an output regulated between 2 and 3 liters per minute. If the animal was not disturbed the reservoir level remained constant, showing that the right ventricular output was keeping pace with the “left” or pump output.

If norepinephrine (which simulates sympathetic vasoconstriction in “physiologic” dosages) was injected into the animal there was not only an increase in vascular pressures but also an increase in the amount of blood in the reservoir. During the action of the drug the animal lost to the reservoir approximately 200 to 300 ml. of circulating blood volume, approximately one-fifth of the total blood volume in the dog. When hexamethonium was injected instead of norepinephrine the pressures fell throughout the vascular system and the animal took up 200 to 300 ml. of blood volume from the reservoir.

It is obvious that following norepinephrine the total vascular volume of the animal decreased approximately one-fifth in order for the excess blood to be “squeezed out” into the reservoir. When the sympathetic impulses were inhibited following administration of the ganglionic blocking agent vascular volume in the animal increased by a similar amount. These changes in vascular capacity were too large to be explained on the basis of arteriolar constriction alone, but must have included postarteriolar vessels as well, that is, capillaries and/or venules and veins. Simultaneous with the rise in pressures following the injection of norepinephrine there was an increase in left auricular drainage and pulmonary arterial pressure reflecting an increase in right ventricular output. It is axiomatic that the right ventricle cannot pump more blood than is delivered to it. Hence, in order to increase its output in the face of a constant output (pump) from the left side, the right ventricle must increase in size by an amount just sufficient to account for the increase in pulmonary arterial pressure


ventricle must have received an increased venous return. This, in turn, was due to the sudden decrease in vascular volume.

These studies demonstrate that sympathetic stimulation produces an integrated response. By decreasing vascular volume, more blood enters the right heart, providing for an increased cardiac output. With sympathetic “blockade,” the opposite effects occurred; there was a fall in right ventricular output, systemic venous pressures and pulmonary arterial pressures, reflecting a decrease in venous return.

Further work has confirmed and extended these findings in man. When hexamethonium was given to hypertensive patients, who were not in heart failure, the arterial pressure fell, and with it there was a commensurate reduction in cardiac output. The pressures in the right auricle, right ventricle and pulmonary artery also decreased, indicating that the reduced output was secondary to a failure of venous return. In the light of the observations in the dog it seems reasonable to conclude that an increase in peripheral vascular volume accounted for the failure of venous return.

The exquisite regulation of vascular volume by the sympathetic nervous system under normal conditions was demonstrated in a simple experiment. The sympathetic vasoconstrictor reflexes were inhibited with hexamethonium in a group of normotensive or hypertensive subjects. Sufficient time was permitted to elapse for stabilization of blood pressure. A phlebotomy then was carried out, following which the blood was reinfused under pressure. With each 50 ml. of blood removed during the bleeding there was a perceptible decline of blood pressure. After removal of only 350 to 500 ml. of blood the arterial pressure had fallen by decrements to collapse levels. During reinfusion the blood pressure rose stepwise with each increment of blood replaced and, when completely reinfused, the level of arterial pressure also had returned to the preinfusion level.

Inhibition of the sympathetic vasoconstrictor reflexes apparently had converted the vasculature into a static system. In this system venous return, cardiac output and, hence, arterial pressure were dependent directly on the effective circulating blood volume. Withdrawals of 50 cc. of blood, or less than 1 per cent of the total blood volume, affected venous return significantly, and removal of less than 10 per cent produced collapse. In the presence of an uninhibited sympathetic nervous system, therefore, minor reductions of effective circulating blood volume (1 per cent or less) activate the baroreceptor reflexes. These reflexes then reduce the vascular capacity by the precise amount required to restore the venous return and cardiac output to the level existing prior to the blood loss.

Effective circulating blood volume may be reduced by means other than hemorrhage. For example, during quiet standing more than 500 ml. excess blood may accumulate in the lower extremities. In the presence of ganglionic “blockade” postural hypotension will result, due to failure of venous return. Measurements of the amount trapped out indicated that postural hypotension induced by drugs occurs not so much because of excessive pooling of blood in the lower extremities but chiefly because of failure of compensatory reduction in vascular volume throughout the body.

Clinical Implications. It has long been known that counterpressure, such as immersion of the lower body in water or application of pressure bandages or pressure suits, will counteract postural hypotension. In this case a reduction in peripheral vascular volume is accomplished by external pressure. It is less generally known that extravascular tissue pressure also can affect vascular volume. Patients with tense edema and hence elevated tissue pressure often are resistant to postural hypotension produced by the ganglionic blocking agents; whereas mercurial diuretics and salt-restricted diets (which deplete extracellular fluid volume) may result in disabling postural hypotension requiring a sharp reduction in dosage of the blocking agent. For this reason, unless the patient is edematous it is advisable to permit moderate amounts of salt in the diet when prescribing the ganglionic blocking drugs. Accumulation of extracellular fluid in the dependent parts of the body occurring nor-


mally during the ambulatory hours of the day may well explain the diurnal fluctuation in sensitivity so often seen in patients who are treated with blocking agents. The dose needed to control the blood pressure in the afternoon and evening often is double and sometimes quadruple the morning requirement.

The role of the sympathetic nervous system and its effects on vascular volume also may have significance in regard to congestive heart failure associated with a low cardiac output. Since in this condition the arterial pressure is normal or elevated despite the reduced cardiac output, it is apparent that the total peripheral resistance is increased. Central venous pressure is elevated, usually out of proportion to the increase in total blood volume, and there is tachycardia. It seems possible that some of these manifestations may be due to stimulation of the sympathetics through the "buffer nerve" mechanisms which are activated by a reduction in cardiac output.

A group of patients with congestive heart failure due to various causes were tested with hexamethonium. The drug was given intravenously in dosages individually titrated so as to produce a significant reduction in arterial pressure. In the patients with hypertensive and arteriosclerotic heart disease, and also in patients with aortic insufficiency, there was immediate improvement in dyspnea and orthopnea as well as a decrease in venous pressure often associated with a fall in heart rate and shortening of the circulation time. As one might suspect, these beneficial results were not observed in cardiac patients with cor pulmonale or mitral stenosis. These changes, as they pertain to hypertensive heart failure, have been confirmed since by other investigators. It was also shown that, in contrast to the hypertensive patient with compensated heart, patients with cardiac failure reacted to hexamethonium with an increase in cardiac output and a significant decrease in total peripheral resistance.

This beneficial effect in congestive heart failure probably is produced by more than one mechanism. Reduction of arterial pressure reduces the cardiac work requirement. Decrease in central venous pressure and hence in right heart filling pressure "unloads" the over-distended right ventricle. In addition, Sarnoff and his coworkers recently have indicated that the heart can perform a given amount of work with less expenditure of energy at low than at high arterial pressures.

This brief review has touched thus far mostly upon personal experiences. There have been many other contributors to the concepts expressed here. Sarnoff, Berglund and Sarnoff demonstrated similar relationships and also have shown by direct measurements that systemic vasoconstriction produces a shift of blood volume to the pulmonary vascular tree, whereas systemic vasodilatation induces a shift in the opposite direction. They emphasized the importance of ganglionic blocking agents in the treatment of pulmonary edema. Several investigators have demonstrated that isolated venous segments in the intact forearm constrict after reflex sympathetic stimulation. Wood, Litter and Wilkins, and also Burch, have found that venous distensibility is decreased in congestive heart failure.

Wood also has demonstrated venoconstriction in the forearm in response to pooling of blood in the legs. Alexander has shown that venomotor tone is increased after hemorrhage.

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The accumulated body of evidence indicates that sympathetic nervous impulses produce constriction not only of the arterioles but probably of the total vasculature. The resulting decrease in vascular volume, by raising filling pressure in the right heart, restores the cardiac output. Thus blood loss from the central circulation, either externally or internally (as in quiet standing) is quickly compensated. This mechanism, which is beneficial in the normal individual, may be detrimental in certain pathologic states—particularly in low output heart failure.

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