Review Article

The Use and Misuse of Pressor Agents

N. Ty Smith, M.D.,* and Aldo N. Corbascio, M.D.†

The last decade has witnessed one of the most dramatic reversals of pharmacologic roles ever undergone by a class of drugs, a process which can be described as the decline and fall of the pressor agent. The reversal was inevitable, the hazardous propensities of adrenergic agents themselves having been clearly perceived by Raab524 as early as 1952. Nevertheless, these drugs still are used frequently in anesthetic practice, since measurement of blood pressure is routine. One of the major pitfalls in the clinical use of such powerful drugs as these is insufficient recognition of the fact that what may be momentarily useful or pharmacologically desirable may turn out to be physiologically unsound. Pressor agents are a good case in point: the uncritical approach to their use has led to frequent disappointment and failure, engendering an attitude of qualified skepticism. The purpose of this review, therefore, is to reconsider the clinical usefulness of pressor agents and, if possible, point to new and more appropriate directives for their use. A description of each agent will be provided under a separate heading to facilitate consultation and retrieval.

Definition

A pressor drug is an agent which elevates blood pressure above the existing level. Pressor agents, then, presumably are used because arterial blood pressure is "too low," although evidence has accumulated that pressure is a poor criterion for use. More than 95 per cent of the information available from Korotkoff sounds is below the audible range.117 Much of this information is lost by improper use of the stethoscope, and much of it varies with the size, type, and application of the cuff. Even more information is lost during conditions when pressure measurement is most critical—during shock, hypothermia, and vasopressor therapy. Thus, all too often criteria for initiating vasopressor therapy, evaluating efficacy, and deciding on discontinuance are based on inaccurate measurement. Even a directly measured blood pressure may be a poor indicator of circulatory status, because tissue perfusion can be excellent when arterial pressure is low; this occurs during peripheral ganglionic blockade. On the other hand, pressure may be elevated, but at the expense of such intense vasoconstriction and poor tissue perfusion that death in a few hours is inevitable if the situation is not corrected. Nevertheless, since blood pressure is an easily obtained measurement, it will remain a guideline to therapy. Too often, however, we choose to correct blood pressure mainly because it is low; we treat the manometer, rather than the patient.

Regulation of Blood Pressure

A simple way to remember the basic regulatory mechanism of the blood pressure is the formula: \( \overline{AP} = CO \times SVR \), where \( \overline{AP} \) = mean arterial pressure, \( CO \) = cardiac output, and \( SVR \) = systemic vascular resistance. Thus, mean arterial pressure may be increased by raising cardiac output, systemic vascular resistance, or both. Cardiac output may be increased by increases in myocardial strength.

* Analogous to Ohm's law in electricity: \( E = IR \), where \( E \) is the voltage (pressure), \( I \) is the current (flow), and \( R \) is the resistance.
heart rate, or the amount of blood presented to the heart, the last usually an increase in venous return to the right side of the heart. Venous return is commonly increased by decreasing the capacity of the veins—that is, by venuconstriction. Systemic vascular resistance is elevated mainly via arteriolar constriction. Very little increase in resistance is achieved by constriction of large arteries.

Vasoconstriction can influence cardiac output in several different ways: 1) arteriolar constriction raises systemic vascular resistance and decreases cardiac output; 2) venous constriction acutely increases venous return and increases cardiac output; 3) precapillary constriction decreases capillary hydrostatic pressure, shifting fluid from tissue to capillaries and resulting ultimately in an increase in cardiac output; and 4) postcapillary constriction increases outflow from the capillaries, causing increased capillary hydrostatic pressure with a loss of fluid from capillaries to tissues, and ultimately decreasing blood volume and cardiac output. Knowing the relative strength of action on each vascular bed guides the selection of a drug. Table 1 shows the average percentage contributions of increments in venous resistance to increases in total resistance (ΔVR/ΔTR × 100). Note, for example, that norepinephrine (Levophed) and methoxamine (Vasoxyl), both considered potent "vasoconstrictors," differ decidedly in their effects on veins. Table 2 shows the relative potencies of several sympathomimetic amines in man with respect to constrictor effects on resistance and capacitance vessels. Again, one finds marked differences among agents.

An excellent discussion of the roles of capacitance vessels and of pre- to postcapillary ratios can be found in a recent review by Zaimis. It would be superfluous to repeat this material, although we shall emphasize and add a few points.

Reflex responses often result in constriction of resistance vessels and dilation of capacitance vessels, or vice versa. In vasovagal syncope initiated in man by orthostasis or negative pressure applied to the lower body, bradycardia and dilation of resistance vessels are responsible for the hypotension. In contrast, it appears that the venous bed, by constriction, tends to maintain filling pressure and, thereby, cardiac output, thus working in the opposite direction. During observations of the reflex responses of the veins in the hind limbs of dogs to baroreceptor and chemoreceptor stimuli and to hemorrhage, differences between the reflex responses of the veins and the resistance vessels to the same stimuli were found. Venous constriction was noted with little or no change in resistance vessels, and vice versa. More strikingly, venous constriction could occur simultaneously with dilation of resistance vessels, and vice versa. Rhythmic fluctuations in pressure of the Mayer and Traube-Hering types were also seen in veins. These responses probably resulted from an increase in activity

<table>
<thead>
<tr>
<th>Agent</th>
<th>ΔVR/ΔTR × 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>13.8</td>
</tr>
<tr>
<td>Tyramine</td>
<td>8.0</td>
</tr>
<tr>
<td>Metaraminol</td>
<td>7.2</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>3.3</td>
</tr>
<tr>
<td>Mephenetamine</td>
<td>1.9</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>1.8</td>
</tr>
<tr>
<td>Methoxamine</td>
<td>1.4</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Resistance Vessels</th>
<th>Capacitance Vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>1.0000</td>
</tr>
<tr>
<td>Metaraminol</td>
<td>0.0874</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>0.0684</td>
</tr>
<tr>
<td>Tyramine</td>
<td>0.0148</td>
</tr>
<tr>
<td>Mephenetamine</td>
<td>0.0049</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>0.0020</td>
</tr>
<tr>
<td>Methoxamine</td>
<td>0.0018</td>
</tr>
</tbody>
</table>

in adrenergic nerves supplying one type of vessel or a decrease in activity in nerves to the other. Examples of this reciprocal behavior were also found in the human forearm by the same authors.56 Baum and Hosko 25 stimulated various areas of the central nervous system in the cat and found that changes in tone of resistance vessels were accompanied by oppositely-directed changes in capillary vessel tone. This was the case whether a pressor or depressor response was obtained. Furthermore, biphasic responses in vascular tone were also seen.

The ratio of pre- and postcapillary resistances can also change with time, even though stimulation remains constant. Evidence indicates that, with the passage of time and in the presence of acidosis,235, 236, 373 arteriolar sphincters lose tone and arteriolar constriction is no longer maintained. However, venous constriction continues, apparently owing to the lower pH at which the venous system normally functions. Relaxation of arteriolar sphincters allows blood to flow into the peripheral circulatory system, but postcapillary or venous constriction hinders return to the heart, and blood is pooled in the peripheral circulation.

Classification of Pressor Agents

The action of vasopressors may be understood better by referring to three classifications: 1) the target organs stimulated (heart vs. blood vessel or central vs. peripheral); 2) the type of action on the receptor sites (direct vs. indirect); 3) the type of adrenergic receptor stimulated (alpha vs. beta).

Heart vs. Blood Vessels

The cardiac actions of pressors are those of increased strength of contraction (positive inotropy) and increased heart rate (positive chronotropy); the blood vessel action is that of vasoconstriction. This is the most useful clinical classification for selecting a pressor. There are no pressor drugs with exclusively central or peripheral actions, although methoxamine and phenylephrine (Neosynephrine) are virtually pure peripheral vasoconstrictors. Most drugs fall in a spectrum ranging from marked central and weak peripheral to marked peripheral and weak central action.

Direct vs. Indirect Action

Direct action implies stimulation of the receptor sites by the drug itself, while indirect action implies stimulation by a secondarily released transmitter substance, such as norepinephrine or isoproterenol. Examples of the direct-acting drugs are epinephrine,149 norepinephrine,119 methoxamine,149 phenylephrine,144 and PLV-2.149 The actions of all other drugs discussed in this review have been attributed at least in part to the indirect mechanism: mephentermine (Wymine),13 amphetamine (Benzedrine),29 methamphetamine (Methedrine),59 metaraminol (Aramine),13 ephedrine,59 and argiotosin.427

The theory of indirect action originated with Burn and Rand,29 who observed that animals pretreated with reserpine, guanethidine or bretylium did not respond to ephedrine, amphetamine, methamphetamine or tyramine. This theory, along with clinical observation, led to the belief that patients under therapy with reserpine or guanethidine would experience severe hypotensive episodes during anesthesia—hypotension which was refractory to many of the pressors.72, 272, 365, 425 This theory was also the basis for the ephedrine response test, which attempted to predict which of the patients on antihypertensive therapy were liable to develop refractory hypotension during anesthesia.44 To perform this test, a standard amount of ephedrine was administered intravenously. A normal pressor response foretold a safe anesthetic course. No response, or a hypotensive response, indicated the discontinuation of antihypertensive therapy for two weeks before selective surgical operation was permissible.

Recent investigations have suggested that patients on reserpine can undergo anesthesia and surgical operation without added hazard.296, 300 and that animals treated with reserpine show no significantly different response to anesthesia from untreated animals.19, 29, 322 Depression of the pressor response to the indirect-acting vasopressors does not occur in the presence of fully effective doses of reserpine, guanethidine, or bretylium.219, 226 Ephedrine definitely has a direct effect of its own.427 Thus, it is usually not necessary to withdraw reserpine or guanethidine before opera-
tion. Furthermore, these patients should usually respond well to all types of pressors. The conflicting results obtained with the epinephrine response test by Crandell and by Hamelberg and Bosomworth are better understood in light of the above information.

The hypothesis of indirect action appears now to be only partially correct. Zaimis has pointed out a number of discrepancies which cast a doubtful light on the whole concept of indirect release. One of the major objections resides in the fact that the pharmacodynamic actions of these agents differ considerably from those one can expect from norepinephrine. For instance, ephedrine seems to be more of a cardiac stimulant than a vasconstrictor, and its bronchodilator actions are much more marked than those of norepinephrine. Methamphetamine has little, if any, peripheral vasconstrictor effect and appears to act mainly on the heart by stimulating rate and force of contraction; hence, it appears to be almost devoid of alpha-receptor activity. It is possible, however, that this agent mobilizes both naturally-occurring catecholamines, by acting on adrenergic nerve endings, and chromaffin cells, adding another source of variability of response. The additional possibility of isoproterenol release is discussed in another section. Ephedrine, however, is able to evoke a response even after total denervation and removal of the adrenal medulla. Its effects persist even after prolonged reserpinization, when all endogenous catecholamines have been depleted. This is often evident in anesthetized patients who have been reserpinized previously. There is also a considerable discrepancy between the metabolic effects of norepinephrine and tyramine. When the two agents were administered in equipressor doses, norepinephrine caused a marked increase in blood free fatty acid and glucose levels, while tyramine's effects were minimal or negligible. Even more puzzling is the response of immunosuppressed animals, in which the pressor effects of tyramine were unchanged, while the cardiac effects were more marked than in control animals. A study by Levine and Sjoerdsma of the ability of catecholamines to precipitate flushing and tryptaminergic crises in patients affected by carcinoid tumors revealed that the most powerful provokers were epinephrine, norepinephrine, and isoproterenol, while indirect-acting agents (tyramine, mephenetermine, and metaraminol) appeared to be much weaker.

One of the main reasons for the existing confusion in this field is the fact that norepinephrine stores in peripheral nerves are not homogeneous, and there is abundant evidence which points to the existence of several norepinephrine compartments whose functional significances and turnover rates are undetermined.

**Alpha- and Beta-Adrenergic Receptors**

This classification is used primarily for sympathomimetic amines. It will be mentioned briefly here, since it is useful in the understanding of pressor action. In 1910, Dale discovered the existence of two components in the mechanism of action of epinephrine by showing that its pressor effects could be blocked and reversed by ergotamine. The physiologic differentiation of norepinephrine from epinephrine was achieved by Von Euler in 1946 and paved the way for a definition of the pharmacologic dissimilarities of these two agents. This led Alhquist in 1948 to postulate the existence of two types of antagonistic adrenergic receptors, which he called alpha and beta. The concept proved to be a felicitous one, as it implied the possibility of selective blockers of these receptors. Indeed, in 1958, Powell and Slater discovered dichloroisoproterenol (DCI), an isoproterenol analog which blocked the hypotensive actions of epinephrine and isoproterenol and antagonized myometrial relaxation and bronchoconstriction in vivo and in vitro. Other more effective beta-adrenergic blockers soon followed, and one of them (propranolol) has been introduced into the clinic.

At present, the elicitation of vasoconstriction, midriasis, retraction of the nictitating membrane, and myometrial contraction is taken as evidence of activation of alpha-adrenergic receptors. The virtual prototype of the alpha-receptor agonist is methoxamine. Activation of beta-adrenergic receptors can produce increased inotropism and chronotropism; ventricular arrhythmias; relaxation of smooth muscles, including arterioles, bronchioles, uterus, stomach, intestine, and bladder; hypergly-
emia, release of free fatty acids; and central nervous system excitation. These effects characterize the pharmacologic actions of isoproterenol, which elicits almost pure beta-adrenergic activation.231

All other catecholamines fit between these two extremes of the pharmacodynamic spectrum, as they are generally endowed with a mixture of alpha- and beta-stimulating properties. Hence, it is presently possible to define the action of a sympathomimetic amine in terms of its preponderance of action, i.e., whether it activates alpha- or beta-receptors, or both. The relative strength of each component is dose-dependent. Thus, epinephrine in very small doses has strong beta- and relatively weak alpha-effects. As the dose increases, alpha-effects predominate.

Individual Pressor Agents

EPIEPHRINE

Although it would seem that epinephrine should not be classified as a clinically-useful pressor agent, it is often used to increase arterial pressure from the ultimate low—cardiac arrest. Its usefulness in this situation has been well documented. Redding and Pearson228 also found in dogs that epinephrine significantly improved survival following hypoxia-induced cardiac arrest; phenylephrine, however, was just as effective. A later study showed that methoxamine and metaraminol, both potent constrictor agents, were also effective, while isoproterenol and mephentermine, agents with good inotropic properties but either vasodilating or weak constricting properties, were of little value.229 Warner,230 was also unable to detect any difference between isoproterenol and a placebo in resuscitating dogs. The surprising conclusion to these studies is that the vasoconstricting effect of epinephrine, rather than the cardiac stimulating properties, is critical for survival; epinephrine, in the large amounts given during cardiac arrest, is a vasoconstricting agent. A possible explanation for this phenomenon is that increased resistance raises arterial pressure during manual cardiac compression, which in turn allows better perfusion of the oxygen-starved myocardium. At low pressures myocardial perfusion is exquisitely pressure-dependent, much of coronary perfusion taking place during diastole. In the study of Redding and Pearson,228 diastolic arterial pressure was significantly greater in the surviving animals. Vasoconstriction also increases venous return. Finally, the oxygen-wasting properties of inotropic agents may be detrimental during this crisis.

Provided a defibrillator will soon be available, an electrocardiogram need not be attached before administration of epinephrine. If ventricular fibrillation is already present, epinephrine will convert a feeble fibrillatory action into a vigorous one, which is more likely to respond to electrical defibrillation.272 In isolated rabbit hearts,251 infusion of epinephrine in amounts sufficient to produce a maximal increase in heart rate did not decrease the fibrillation threshold to electric shock, even in the presence of chloroform.

The vascular effects of epinephrine are the algebraic sum of the simultaneous activation of alpha- and beta-adrenergic receptors. With larger doses, the alpha receptors predominate, and a pressor response ensues. Hence, when used as a resuscitant, epinephrine is likely to act in this fashion, but if it gains access to the circulation in small amounts (local anesthesia, epidural or brachial block), its peripheral beta-adrenergic stimulating actions come to the fore, vascular resistance is decreased and, in spite of a concomitant increase in cardiac output, hypotension may follow.290 For this reason, epinephrine may accentuate rather than antagonize the decrease in systemic arterial pressure due to sympathetic blockade.290 When epinephrine is used with lidocaine to institute a brachial block, cardiac output often is increased, and peripheral resistance is diminished, while arterial blood pressure remains unchanged.290

The ability of epinephrine to activate beta-adrenergic receptors may be clinically relevant when it is used as a local vasoconstrictor in epidural anesthesia for obstetrical purposes. In this instance, epinephrine is likely to produce uterine relaxation, a response which may noticeably influence the course of labor. This epinephrine-induced inhibition of uterine contraction was described for the first time by Rucker,247 in the course of studies of caudal anesthesia. Two years later, in a subsequent study, this author advocated the use of epi-
nephrine as a uterine relaxant. The effects of epinephrine on uterine contractility were subjected to further investigations by Bourne, Woodbury, and Brown and Wilder. These investigators found that the intravenous injection of 60 to 150 μg epinephrine induced a biphasic response, an initial increase in uterine tone followed by relaxation. These results were confirmed by Woodbury and Abreu, who also noted that the administration of a smaller dose (20 μg during 6 to 10 minutes) induced relaxation only. The response of the pregnant uterus is dependent on the dose, rate and route of administration and is influenced by the baseline activity of the organ at the time of administration. In patients in labor who have not received any analgesics, epinephrine decreases considerably the degree of discomfort and pain, a response which is related to the degree of inhibition of uterine tone. Often this is followed by a rebound increase in symptoms. Zuspan and his associates studied the effect of epinephrine on the pregnant uterus at term by measuring amniotic pressure through a transabdominal catheter. They ascertained that the infusion of epinephrine at rates of 0.05 to 0.25 μg/min had no effect on uterine contractility. When the rate was increased to 5 μg/min, uterine activity diminished within three minutes, this state of inertia persisting throughout the period of administration and for 20 minutes thereafter. An increase of the rate to 10 and then to 20 μg/min in patients in induced labor was followed by a progressive decline in activity. In contrast, in patients in spontaneous labor, an increase in the rate of infusion from 5 to 10 to 20 μg/min produced no further decrease in tone.

Recent studies have demonstrated the clinical significance of these observations. Gunther and Bauman, in the course of a well designed double-blind study, found that the addition of epinephrine to the local anesthetic mixture introduced into the caudal canal prolonged the first stage of labor and doubled the number of patients who required oxytocic supplementation.

**Norepinephrine**

Although norepinephrine still retains its title as "the" neurohumoral mediator of the sympathetic system, a recent hypothesis states that norepinephrine release is secondary to a preliminary release of acetylcholine (ACh) at the endings of adrenergic fibers. The intermediary role of ACh is suggested by a number of experimental observations: 1) the fact that ACh can be released from sympathetic trunks, which are known to contain almost exclusively adrenergic fibers; 2) the ability of ACh to mimic the actions of norepinephrine when its muscarinic actions have been blocked by atropine; 3) the fact that ACh induces piloerection when injected into the skin as well as vasoconstriction when infused into the atropine-treated rabbit ear. These effects are abolished by sympathetic denervation or reserpine pretreatment. Even more significant is the fact that hemicholinium, which blocks the synthesis of ACh, can reduce or block the response of sympathetic fibers to electrical stimulation. A similar effect can be induced by the exposure of sympathetic fibers to botulinus toxin, which interferes with ACh liberation. Elucidation of the exact chain of events awaits further experiments.

The vascular actions of norepinephrine, in the clinical doses usually employed, are the resultant of the simultaneous activation of alpha- and beta-adrenergic receptors in the heart and in the resistive and capacitance components of the vasculature, with a marked predominance of alpha-stimulating action. When administered intravenously, norepinephrine increases the force and, vagus permitting, the rate of myocardial contraction. Peripheral resistance and diastolic and systolic pressures are increased. These actions are by no means selective, in the sense that only myocardial beta-adrenergic receptors and peripheral alpha receptors are activated. Actually, Glover and Hutchinson have presented evidence pointing to the stimulation of beta as well as alpha receptors in human forearm vessels. Propranolol augments the vasoconstrictor response to the local infusion of norepinephrine, although the beta or vasodilator component of the peripheral vascular response of norepinephrine is practically negligible and activation of alpha receptors, and hence vasoconstriction, prevails. Large doses of an alpha-blocking agent are indeed necessary to prevent the vasoconstrictor actions of norepinephrine.
In man its effects on the resistance and capacitance vessels are the greatest obtainable with any sympathomimetic amine. In normal and splenectomized dogs, the marked venoconstriction will cause a significant centripetal shift of circulating blood volume. A similar effect has been observed in man and a considerable increase in cardiopulmonary load takes place. In the normal heart, heterometric autoregulation (the Frank-Starling mechanism) may prevent dangerous increases in pulmonary arterial and left atrial pressures and eventual pulmonary edema. A damaged heart, however, may not be able to handle the simultaneous increases in venous return, pulmonary volume, and outflow tract resistance with equal ease; hence the administration of norepinephrine to mature patients should always be guarded even in the absence of evidence of cardiac disease.

A relatively common side-effect of norepinephrine is tissue necrosis and sloughing, which can occur with or without accidental extravasation. The cause of the necrosis upon suffusion of subcutaneous tissue with norepinephrine is sustained vasoconstriction and prolonged tissue anoxia; this can be prevented by using an alpha-blocker (5 to 10 mg phentolamine per 4 mg norepinephrine) in the infusion bottle.

The mechanism of action in areas of necrosis distant from the site of administration of the drug is more difficult to explain and seems to depend on several factors, such as rate and duration of infusion and individual susceptibility. These necroses are the tangible and visible signs of the profound parenchymal damage that can be induced by prolonged administration of pressor doses of norepinephrine. Raab, Rona, and Chappel have documented fully the necrotizing actions of catecholamines on the heart. The production of such lesions may be secondary to vasoconstriction, leading to drastic reduction in blood flow through the organ, damage to the intima of capillary vessels, circulatory stasis, acidosis, increased capillary permeability and, ultimately, necrosis. The heart is particularly susceptible to the necrotizing action of norepinephrine on at least two counts: interference with microcirculation in the myocardium, and intramural shearing effect on the vessels and myofibrils due to the intense mechanical stimulation of the cardiac muscle. The latter mechanism, which is operative in skeletal muscle, has not been adequately pursued as one of the causes of myocardial failure after the infusion of excessive doses of epinephrine or norepinephrine, in spite of the fact that as early as 1905 Ziegler showed that repeated injection of small doses of epinephrine could induce cardiac lesions in a large percentage of animals. The cardiotoxic and necrotizing actions of exogenously administered epinephrine were confirmed two years later by Josue.

The problem has been re-examined more recently by Nash and Carter. They administered epinephrine and norepinephrine to dogs (10 μg/kg/min) for two hours and found that such doses would cause irreversible deterioration of the cardiovascular status of the animals, with a 25-30 per cent decrease in blood volume, a corresponding increase in hematocrit, and a decreased blood pH. The heart, the stomach, the diaphragm, the intestine, and the urinary bladder and gallbladder showed signs of gross hemorrhagic damage. The initial abrupt rise in blood pressure was followed by a steady decline and a fall below preinfusion levels within two hours. Indeed, it has been shown that the prolonged infusion of norepinephrine can produce a state of shock indistinguishable from hemorrhagic, traumatic or endotoxic shock. It has been shown also that cardiac failure can be induced in dogs with as little as 2-4 μg/kg/min norepinephrine administered for 30 to 60 minutes. In dogs, heart failure has even been induced with infusions of norepinephrine too small to produce a pressor response. The failure is partly due to subendocardial hemorrhages and extensive foci of necrosis and myofibrillar degeneration. This response is dose- and time-dependent and bears a striking resemblance to the myocardial lesions commonly observed in human coronary artery disease. It is perfectly possible that catecholamines play a decisive pathogenetic role in coronary artery disease. This hypothesis was seriously entertained by Raab in 1954 and appears to be an important concept in view of the beneficial effects that catecholamine depleters, adrenergic agents, and beta-adrenergic blockers seem
to display in human coronary artery disease. The improvements induced by propranolol in the cardiac status of patients with angina may be only partly due to the hemodynamic advantage induced by the drug: bradycardia with consequent increase in diastolic minute time and improved coronary perfusion. A more subtle sparing effect on myocardial microcirculation and a possible molecular effect on cardiac oxygen consumption may also be involved.

The dangers of catecholamine-induced cardiomyopathy recently have been reappraised by DeFauw and Burch. They asked how normal are hearts transplanted from donors who have sustained cerebral damage. This damage is likely to evoke a "sympathetic storm," with massive mobilization of endogenous catecholamines. The electrocardiographic abnormalities seen in such patients (high T-waves) can be reproduced by the intracoronary injection of norepinephrine, epinephrine, nicotine, or lycopodi um spores. The possibility of the late effects of catecholamine administration has not yet been considered, though there is a real possibility of inflicting damage which will not be immediately evident but may prejudice the cardiac future of the patient by inducing self-perpetuating subliminal lesions.

Another liability of the clinical use of norepinephrine is its ability to induce hyperkalemia, as well as metabolic acidosis, by release of free fatty acids. The sudden increase in plasma potassium coincident with hemorrhage or reabsorption of necrotic tissue (postpartum bleeding or extensive burns) could precipitate cardiac arrest.

Tachyphylaxis can occur with norepinephrine, although not so frequently as with ephedrine or metaraminol. Several hypotheses to explain its occurrence have been entertained: 1) Norepinephrine can accumulate in sympathetic ganglia or at the neuroeffector junction. The mechanism in this case would be analogous to that observed with MAO inhibitors, namely, accumulation of an excess of the mediator or some of its inactive or less active metabolites. 2) Systemic acidosis due to anoxia, hypotension, and circulatory stasis can occur. The mechanism of the refractoriness is far from clear, though it is readily observable in animal preparations. 3) The formation of an endogenous vasodilator, possibly a kinin or an isoproterenol-like substance, has been proposed, although scantily documented. 4) More intriguing is the possibility that receptor saturation by the mediator may by itself cause blockade and refractoriness of vessels. An analogous situation is known to occur with ACh at the endplate, where an excess of the mediator leads to neuromuscular paralysis. The work of Mazurkiewicz and Murnaghan, who used hexamethonium and catecholamines with greater ganglionic blocking properties than norepinephrine, seems to discount the possibility that ganglionic blockade or the release of an isoproterenol-like substance can explain norepinephrine refractoriness. Restoration of normal pH following norepinephrine-induced acidosis seems to have little effect on the phenomenon.

Freeman suggests that the profound loss in plasma volume is responsible in some instances for norepinephrine refractoriness. Its prevention with an alpha-adrenergic receptor blocker, such as phenolamine, or by blood replacement suggests that the increase in postcapillary (venular) resistance hastens the efflux of plasma from the circulation, with a consequent decrease in volume and a conspicuous increase in blood viscosity. It would be pertinent, then, to test whether such conditions can be prevented by the administration of substances, like low-molecular-weight dextran, which modify the rheological characteristics of circulating erythrocytes by decreasing the surface charge of the corpuscular membrane.

Some teleological considerations may help in the understanding of the clinical limitations of norepinephrine, which was perhaps never meant by nature to be poured intravenously in such enormous concentrations. There are good reasons to believe that norepinephrine release in a physiologic context is a far more discrete and carefully modulated process, available to assist in day-to-day activi-

---

* This phenomenon is analogous to the fall in blood pressure often observed after removal of a pheochromocytoma. This drop is preceded by excess serum norepinephrine levels and by a decrease in erythrocyte volume and can be prevented by pretreatment with phenolamine or by excess blood volume replacement.
ties, such as regulation of regional circulation. It has been suggested that the large quantities secreted during hemorrhage or trauma in the wild state are pathologic and detrimental to the animal. Even in its less dramatic role, the possibility still exists that endogenous catecholamines represent one of the most serious limitations and potential risks to the biological design of the mammalian heart.

**Metaraminol**

Metaraminol possesses effects similar to those of norepinephrine, stimulating both alpha- and beta-adrenergic receptors, with a preponderance of alpha stimulation.\(^{29,272}\) Norepinephrine acts directly, while metaraminol may act both directly and indirectly by the release of norepinephrine.\(^{46}\) The latter hypothesis is strengthened by the fact that after metaraminol is administered, the radioactivity issuing from a heart labelled with tritiated norepinephrine appears almost entirely as bases (norepinephrine and normetanephrine), suggesting that metaraminol, like guanethidine, releases norepinephrine from the granules.\(^{59}\) Metaraminol is an exceedingly potent depleter of norepinephrine in peripheral vessels\(^{25,221}\) and atria.\(^{25,46}\) Since metaraminol is dependent for much of its action on the release of norepinephrine, these data help explain the commonly observed tachyphylaxis\(^{55}\) and the loss of the positive chronotropic response to hypotension.\(^{45}\) By depleting norepinephrine stores in sympathetic nerve endings in the heart and blood vessels, prolonged infusions of metaraminol may result in a diminution of sensitivity to subsequently administered metaraminol. Discontinuing metaraminol and infusing norepinephrine restores the response to metaraminol,\(^{46}\) suggesting as a mechanism the repletion of norepinephrine stores at the sympathetic nerve endings.

The release and depletion of norepinephrine is due to the replacement of norepinephrine at the nerve endings by metaraminol itself.\(^{55}\) This property is similar to that postulated for the metabolic products of alpha-methyltyrosine (Aldomet), an antihypertensive agent.\(^{173,217}\) Originally, it was assumed that alpha-methyltyrosine decreased endogenous levels of catecholamines by inhibition of decarboxylase or dopamine-beta-hydroxylase. The reac-
duction is now known to result from the displacement of norepinephrine by amine metabolites.\(^{12,122,232}\) These compounds consequently are available for release by stimulation of sympathetic nerves or by drugs such as tyramine. Thus, they may act as "false transmitters" in place of norepinephrine.\(^{38,50}\) Metaraminol, however, is much weaker than norepinephrine. It is, in fact, \(1/2\) as potent as norepinephrine in constricting resistance vessels and \(1/2\) as effective in reducing the caliber of capacitance vessels.\(^{224}\) Therefore, the effect produced by its release is proportionately less. This suggests that metaraminol, like alpha-methyltyrosine, might be useful as an antihypertensive agent. Indeed, Crout and co-workers\(^{66}\) have successfully used metaraminol orally to lower blood pressure in hypertensive patients. Thus, paradoxically, a potent vasopressor can also combat hypertension.

Although metaraminol is not a substrate for MAO or COMT, it mimics norepinephrine in many respects at the adrenergic terminals.\(^{216}\) Tritiated metaraminol can be depleted from nerve endings by guanethidine, just like norepinephrine.\(^{24}\) In rats injected intraperitoneally with large amounts of alpha-methyl-
-tyrosine, metaraminol is both formed and excreted.\(^{201}\) However, only under certain conditions is a one-for-one displacement of norepinephrine by metaraminol observed.\(^{211,213}\) This uptake phase of retention of tritiated metaraminol requires sodium and potassium in the external medium, plus an energy source. This energy source can be provided by glycolysis.\(^{214}\)

Because of more gradual onset and prolonged duration of action, maintenance of blood pressure with metaraminol is generally smoother than with norepinephrine. After arterial pressure has been raised to an effective level by its intravenous administration, treatment with the drug by intermittent subcutaneous intramuscular injection can continue, since metaraminol is less likely to cause ischemic necrosis. Subcutaneous necrosis after administration of metaraminol has been reported, however.\(^{66}\) The prolonged action of metaraminol can be a disadvantage, since accidental hypertension is more likely to cause damage.
Although metaraminol can increase the force of contraction of the heart, the end-result in normal subjects, as with norepinephrine, appears to be either no change or a reduction in cardiac output. The increases in systolic and diastolic pressures usually are accompanied by marked reflex bradycardia, which can be abolished by atropine. Cardiac output in turn increases strikingly when reflex bradycardia is prevented by atropine. On the other hand, in patients with hypotension and clinical features of shock, metaraminol can elevate cardiac output and peripheral resistance simultaneously. Further increases in dose produce additional increments in peripheral resistance without affecting cardiac output.

**Methoxamine**

Methoxamine is a near-prototype of a pure vasoconstricting, or alpha-adrenergic stimulating drug. The initial therapeutic claim which ushered in its extensive clinical use was based on this property, particularly the resultant absence of direct cardiac stimulating actions. It was considered highly suitable for countering hypotension during high spinal anesthesia and it was the agent of choice to raise systemic arterial pressure in cardiogenic shock.

Indeed, since methoxamine exerts its stimulating actions almost exclusively by its ability to induce a maximal increase in peripheral resistance, one sees a dramatic pressor response.

Unlike most of its catecholamine congeners, it is actually devoid of positive inotropic actions on the myocardium, and its cardiac effects seem to be limited to some mild antiarrhythmic and myocardial depressant properties.

There is incontrovertible evidence that methoxamine, in high doses, may exert an adverse effect on cardiac contraction. The drastic activation of the baroreceptor system induced by a steep elevation of diastolic pressure and diminished aortic runoff induces a vagal discharge the intensity of which often reflects itself unfavorably on myocardial function. Brewster found that he could induce left ventricular failure in dogs by the continuous administration of methoxamine. Indeed, the action of methoxamine on the resistance vessels is so drastic as to be comparable to the application of a pharmacologic clamp or an obstruction balloon in the aorta. It seems also that the pressor effects of methoxamine are detrimental even in the normal heart. Duke has shown that methoxamine caused increases in cardiac work, peripheral resistance and central blood volume, with signs of a marked decrease in blood flow to tissues. The increase in left ventricular load entails an increase in oxygen consumption, which reflects unfavorably on cardiac function by increasing ventricular work and decreasing the overall efficiency of the heart. Goldberg studied the effects of methoxamine (34–120 µg/kg intravenously) in seven patients undergoing cardiac surgery. In five of these patients, methoxamine did not significantly depress cardiac performance. In the remaining two, cardiac contractile force appeared to be slightly increased. Doses of methoxamine which increased diastolic pressure to 33 torr above the pre-existing level invariably increased cardiac size in intact anesthetized men. It appears, therefore, that the marked increase in outflowtract resistance without a concomitant effect on the ability of the myocardium to shorten and develop tension induces a conspicuous increase in ventricular end-diastolic size. This increase in dimension, especially systolic volume, could explain the increase in stroke and, occasionally, cardiac index seen with this drug, though it is obvious that this is the least desirable method by which to increase cardiac output.

The hemodynamic effects of methoxamine have also been re-examined recently by Smith and Whitcher, who administered methoxamine in a single intravenous dose of 0.65 mg/kg before and after the administration of atropine to five normal subjects. Cardiac output was measured continually with a ballistocardiograph–analog computer system. Methoxamine induced marked depression of heart rate, cardiac output and left ventricular work and a moderate decrease in stroke volume. Peripheral resistance was markedly increased even with a moderate increase in diastolic pressure. These depressant effects were ameliorated by atropinization. The duration of the effect of a single, small intravenous dose of methoxamine is relatively short, but the depression of cardiac function and the increase in peripheral resistance may be particularly
harmful in elderly patients or those with cardiac disease.

Udhoji et al.\textsuperscript{205} have observed that methoxamine can reduce venous return and favor peripheral pooling of blood. This is another unusual and undesirable feature of the pharmacodynamic actions of methoxamine which would tend to contraindicate its use to antagonize hypotension consequent to sympathetic blockade induced by high spinal anesthesia.

It appears that an adequate level of ionized calcium is a prerequisite for the pressor actions of methoxamine. Ellis\textsuperscript{188} has shown that the simultaneous administration of EDTA (ethylene diaminetetraacetic acid), a calcium chelating agent, will reverse the pressor effects of the drug and induce signs of cardiac failure—mechanical pulsus alternans without electrocardiographic signs of alternation. He attributes this response to uncoupling of excitation-contraction processes in the heart and in vascular tissue. It is well known that the presence of ionized calcium is essential for optimal myocardial contraction, and hypocalcemia induced by the administration of large amounts of citrated blood is far from rare in surgical situations.\textsuperscript{27, 29} This dependence on optimum calcium levels for the development of the pressor actions of methoxamine is another unsuspected liability of this agent. To what extent the pressor actions of other catecholamines are calcium-dependent has not been fully explored; it is possible that this liability extends to the entire spectrum of pressor agents.

Methoxamine has a modest antiarrhythmic action. It was apparent early that this action was not due to a carotid sinus-vagal reflex from hypertension, since ventricular arrhythmias are affected\textsuperscript{223} and the effect persists even after section of the vagus.\textsuperscript{193} These antiarrhythmic properties of methoxamine may be due to a weak beta-blockade of cardiac adrenergic receptors. About 30 chemical congeners of methoxamine which do not possess pressor actions have been shown to have the same antiarrhythmic properties.\textsuperscript{109} Cardiac beta-adrenergic blocking properties have been detected in methoxamine and isopropylmethoxamine.\textsuperscript{2, 187, 190, 238, 260} Other properties of methoxamine could also be responsible for the antiarrhythmic effect. Methoxamine prolongs the absolute refractory period of the heart, raises the threshold to electrical stimulation, and depresses atrioventricular conduction.\textsuperscript{126} Ellis\textsuperscript{151} has filed a dissenting opinion, however. He believes that the antiarrhythmic actions of methoxamine are due neither to beta-blockade nor to reflex or direct changes in cardiac excitability, and maintains that the exact mechanism of this property is obscure and still open to question.

**Phenylephrine**

In a previous review,\textsuperscript{26} we stated that methoxamine and phenylephrine were virtually identical, each eliciting pure alpha-stimulating effects, that is, vasoconstriction without any cardiac effect. However, as described above, methoxamine can depress the heart slightly and may possess antiarrhythmic properties; phenylephrine can stimulate the heart to a slight degree and may possess some antiarrhythmic action. These properties of phenylephrine have been attributed to a previously unsuspected alpha-adrenergic stimulating effect on the heart.

It has been known for some time that phenylephrine augments myocardial contractile force.\textsuperscript{21, 23, 141, 144, 415} This effect has been generally disregarded, although Waldhausen et al.\textsuperscript{140} were able to show a 20 to 25 per cent increase in myocardial contractile force in dogs. Covier\textsuperscript{150, 153} demonstrated subsequently that this positive inotropic effect was reversed by the alpha-adrenergic blocking agents phenoxybenzamine or phentolamine, rather than by the beta-adrenergic blocker propranolol. They concluded that alpha receptors, hitherto believed absent in the heart, do exist and mediate positive inotropy. Strengthening this hypothesis is the fact that a significant component of the positive inotropic effect of epinephrine can be antagonized by phenoxybenzamine or phentolamine, but none of the inotropic effect of isoproterenol can be so antagonized. However, phenoxybenzamine and phentolamine suffer from the same operational disadvantage which led to the abandonment of the original beta-adrenergic blocking agent, dichloroisoproterenol, that is, they can stimulate beta-adrenergic receptors and hence increase cardiac inotropy.\textsuperscript{154} Therefore, these results must be interpreted with caution.
As with methoxamine, the basis of the antiarrhythmic action of phenylephrine was originally thought to be reflex vagal activity. However, phenylephrine prolongs the functional refractory period in isolated guinea pig atria. This is a quinidine-like effect, although, unlike that of quinidine, it can be reversed by phenoxybenzamine, and thus has been attributed to an alpha-adrenergic stimulating action.

Alpha receptors may also be present in the sinoatrial node. Methoxamine and isopropylmethoxamine produced a negative chronotropic effect when selectively administered into the artery perfusing the sinus node. This effect can be reversed by phentolamine or phenoxybenzamine. Similarly, the latter two agents enhance the positive chronotropic effect of norepinephrine or tyramine. Again, it is possible that the beta-stimulating properties of the alpha-blocking drugs may have influenced these results.

It is apparent that there are several differences between methoxamine and phenylephrine. These differences can be detected in normal subjects. Methoxamine administered after atropine reduces stroke volume, whereas phenylephrine given after atropine does not affect stroke volume. It is doubtful whether these differences are clinically significant.

Phenylephrine in dogs increased myocardial oxygen uptake, but only in doses that caused a significant increase in arterial pressure. This increase in oxygen uptake appeared to be proportional to increased cardiac work, hence phenylephrine was not considered to be an "oxygen-wasting" sympathomimetic amine, in the same class as norepinephrine and isoproterenol. Phenylephrine also produced hyperglycemia, but did not change plasma levels of nonesterified fatty acids.

**Ephedrine**

Ephedrine manifests cardiac stimulating and mixed peripheral vascular effects, with cardiac effects predominating. Thus, tachycardia, increased cardiac output, and increased stroke volume are commonly observed after administration of ephedrine. In spite of the marked inotropic effects, the incidence of arrhythmias from ephedrine administered during general anesthesia is not so great as with many other centrally-stimulating amines.

The direct peripheral vascular effects of ephedrine have been studied in man. Cohn noted increases in heart rate and cardiac output and a decrease in forearm vascular resistance following intravenous administration of ephedrine. Direct infusion into the brachial artery decreased forearm blood flow at lower rates of infusion (40–100 μg/min) and produced variable responses at higher rates (100–2000 μg/min). Frewin and Whelan infused ephedrine into the forearms of human volunteers at rates of 24 to 200 μg/min and observed a predominantly vasoconstricting effect which was mediated by release of a constrictor substance from the sympathetic nerve endings acting on alpha-adrenergic receptors of vascular smooth muscle. A second effect was vasodilation, which was unmasked when alpha receptors were blocked by intra-arterial phentolamine or when the sympathetic nerves were absent. This effect was thought to be due to a direct action of ephedrine on betaadrenergic receptors. Mild vasoconstricting effects were seen in the limb following blockade of both alpha- and beta-receptors or following sympathectomy.

Theoretically, ephedrine is a good choice to antagonize hypotension consequent to sympathetic blockade induced by spinal or epidural analgesia. This blockade causes venous pooling, decreased peripheral resistance, decreased cardiac output, occasionally decreased myocardial contractility, and decreased heart rate. Ephedrine acts almost as a physiologic antagonist to each of these depressant actions.

However, it is not an absolutely reliable drug; that is, it does not always elicit a satisfactory pressor response, and tachyphylaxis quickly ensues after repeated injection. The causes of this tachyphylaxis are unclear. It is tempting to attribute it simply to depletion of catecholamines from the adrenergic nerve endings. However, the quantitative role of the release mechanism in the action of ephedrine is not certain. Parks et al. could detect no constricting effect of ephedrine in five to ten times the normal dose in two patients with autonomic degeneration and in two fol-
lowing surgical sympathectomy. On the other hand, Mills and Moran 37 found that the myocardial and vascular stimulating effects of ephedrine were not suppressed by acute or chronic pretreatment with reserpine in anesthetized open-chest dogs. To add to the confusion, Goldberg and Shideman 44 uncovered evidence in cat papillary muscle that ephedrine may release acetylcholine or an acetylcholine-like material. In very high concentrations (10^{-3} M) ephedrine produced a negative inotropic effect which was blocked by atropine. Beta-adrenergic block changed the positive inotropic response to a negative one. Physostigmine decreased the positive inotropic response produced by ephedrine at certain concentrations.

The various isomers of ephedrine produce various degrees of tachyphylaxis 213 which are not correlated with the amount of norepinephrine released from the isolated rat heart. 1 Studies with D(-)-ephedrine 44, 96, 207 indicate that catecholamines are not significantly decreased during or after tachyphylaxis. Biochemical 50 and pharmacologic 211, 212 studies indicate that isomers of various amines possess different affinities for catecholamine uptake sites. If a given “indirect-acting” amine has a greater affinity for the uptake sites (or transfer sites), and is not washed off the tissue during perfusion, it may inhibit its own uptake during subsequent injections. This will result in decreased displacement of catecholamines from storage sites and the consequent diminishing of tissue response. 1, 37, 148 In other words, different rates of onset of tachyphylaxis may be indicative of an amine’s ability to prevent its own uptake into the sympathetic nerve endings. Consonant with this view is the fact that in isolated rat and guinea pig atria, the positive inotropic effects of both exogenous epinephrine and endogenous norepinephrine were suppressed by ephedrine in high concentrations. 282 In addition, ephedrine enhances the effects of direct-acting amines in low doses and blocks their effects at high doses 72 in cardiac phosphorylase a. It was felt that the effects of ephedrine can be explained on a dual basis; ephedrine blocks amine uptake (cataleptic-like effect) and occupies and blocks beta-adrenergic receptors.

Mephenetermine, Methamphetamine, and Hydroxyamphetamine

These drugs show a predominance of cardiac stimulation over vasoconstriction, but probably only at low dose levels. The last two are not ordinarily used as pressors because of their “side-effects” of cortical stimulation. Mephenetermine possesses cortical stimulating properties, although considerably less than the other two drugs. Andersen and Gravenstein 11 reported mild euphoria in three of six normal subjects in whom mephenetermine was used as a pressor. We have noticed the same phenomenon in five of six subjects.

Initially mephenetermine was considered to be a vasoconstrictor. 25, 114 Later, some investigators regarded it as a weak vasodilator. 24, 25 This could be a reason for a theoretical preference in the treatment of hypotension. However, recent studies in isolated perfused limbs have demonstrated a predominantly constricting action. 25 Li and co-workers, 22 in studies of normal conscious man, found no significant changes in total peripheral resistance for the first 20 minutes after injection of mephenetermine, with vasoconstriction supervening subsequently. Perhaps the delayed appearance of vasoconstriction was a secondary response mediated by a sustained release of catecholamines. Andersen and Gravenstein 11 noted an increase in total peripheral resistance for the first 20 minutes, with a subsequent return to control levels. After injecting large amounts of mephenetermine (0.75 mg/kg) intravenously into volunteer subjects, we observed an increase in systemic vascular resistance to as much as twice control values, appearing within three minute and lasting more than an hour (Smith, N. Ty, unpublished data).

Of considerable importance is a pronounced increase in venous return noted with mephenetermine. 294, 411 Isoproterenol, a known cardiac stimulant and vasodilator, was the only other agent studied that possessed such a property. Udhoji and co-workers 305 postulated that this increase could be due either to direct venous constriction or to the opening of small veins beyond which relatively large quantities of blood may be pooled. Horsley and Eckstein 12 observed venous constriction in man after administration of mephenetermine and
concluded that the drug might produce an increase in cardiac output by extruding blood from the extremities.

Many of the observed differences in effect on peripheral vessels may be due to differences in species, doses, initial conditions, and preparations. For example, Li and co-workers reported that, in patients with sympathetic block produced by spinal anesthesia, the effects of mephenetermine depended upon the state of the cardiovascular system: if the cardiac output was low, the pressor effect was due mainly to an increase in cardiac output; if total peripheral resistance was low, the pressor effect was brought about by an increase in total peripheral resistance. This seems to be a desirable way to produce a pharmacologic effect.

In contrast to the confusion about the vasoconstricting properties of mephenetermine, no one has disputed its excellent positive inotropic action. This property has been observed in dogs, and man.

We have noted that the agent has a more prolonged action than had been previously suspected (Smith, N. Ty, unpublished data). Ninety minutes after the intravenous injection of mephenetermine in normal human subjects, atropine, 1–2 mg, administered intravenously, produced dramatic increases in mean arterial pressure, cardiac output, and left ventricular minute work. The repeat injection of mephenetermine 15 minutes later produced little change, suggesting that the maximum effect of the agent was still present.

Mephenetermine manifests strong pressor effects if administered during or shortly after infusion of norepinephrine in reserpine-treated animals. A previous dose of cocaine or mephenetermine can block this response. Two explanations for this phenomenon are possible: 1) mephenetermine has a pressor action of its own which needs minimal amounts of norepinephrine and another substance liberated from tissue stores of catecholamines; 2) mephenetermine liberates norepinephrine from an exceedingly labile store which can be filled by minute amounts of norepinephrine, but which is optimally close to receptor sites.

Another feature of this fascinating drug is its antiarrhythmic property. Almost invariably a positive inotropic effect is associated with an arrhythmogenic effect. Mephenetermine is one of the few exceptions.* Most of the antiarrhythmic action of mephenetermine is due to its effect on the conduction system of the heart—decreased conduction time in the bundle of His and the Purkinje system, decreased atrioventricular conduction time, and a decrease in the refractory period of the atrium. This antiarrhythmic property has been noted in isolated hearts; in certain arrhythmias produced by acetylcholine in dogs; in isolated guinea pig atria; in arrhythmias produced by ligation of the anterior descending coronary artery in dogs; in spontaneous ventricular fibrillation during hypothermia in dogs; in nodal rhythms, supraventricular tachycardia, bigemini and premature ventricular beats in man; and in the arrhythmias accompanying the shock of myocardial infarction. However, mephenetermine has shown no protective effect against arrhythmias caused by a combination of cyclopropane and epinephrine. In another series, mephenetermine could not prevent ventricular fibrillation induced by manipulation of the heart during hypothermia. One group claims that mephenetermine actually can precipitate arrhythmias during cyclopropane anesthesia in dogs. Another that mephenetermine induces ectopic foci, abnormal beats, and abnormal responses to test stimuli in dogs. Gilbert and co-workers also detected a moderate increase in irritability to multiple stimuli. However, they also noted this tendency with methoxamine, whose antiarrhythmic action is undisputed.

**ANGIOTENSIN**

Angiotensin is a pressor octapeptide derived from renin, an enzyme present in the juxtaglomerular cells of the kidney. Renin, upon release into the bloodstream, undergoes a two-stage process of enzymatic cleavage, yielding an active octapeptide: angiotensin II.

The juxtaglomerular cells contain conspicuous cytoplasmic granulations, which are discharged into the bloodstream in response to appropriate physiologic stimuli: changes in volume, pressure, and dp/dt in the afferent arteriole.
glomerular artery. Thus, these cells behave like a physiologic flowmeter.\textsuperscript{126, 204}

The principal physiologic action of angiotensin is to promote the secretion of aldosterone from the zona glomerulosa of the adrenal cortex. Aldosterone is the most active mineralocorticoid. Angiotensin, then, constitutes the main link of the homeostatic mechanism that regulates sodium reabsorption, blood volume, and arterial blood pressure.\textsuperscript{202}

The pharmacodynamic actions of angiotensin, which are usually elicited by doses of the peptide which are relatively small but clearly unphysiologic, are partially mediated at the periphery by adrenergic fibers and the perivascular chromaffin system. The details of this action are not always clear in all species and experimental situations, though it appears that angiotensin II may facilitate the release of norepinephrine from sympathetic nerves\textsuperscript{422} or block the re-entry of newly released norepinephrine from these nerve endings.\textsuperscript{20, 307, 306, 414} Pals\textsuperscript{203} has adduced convincing evidence of such an action of angiotensin on alpha-adrenergic receptors in rats. He also found that treatment with bretylium tosylate, which blocks adrenergic neurons, enhances the pressor effects of angiotensin as well as those of phenylephrine, an alpha-adrenergic receptor stimulant. Other possible effects of angiotensin are direct musculotropic effects and stimulation of sympathetic ganglia. All of these mechanisms have been discussed in great detail by Zaimis\textsuperscript{427} in a recent review which appeared in this journal.

Gascon and Vailancourt\textsuperscript{127} have shown that the stimulant effects of angiotensin and tyramine on the isolated guinea pig seminal vesicle are mediated by the release of extraneural stores of catecholamines located in the smooth muscle cells. This view has been challenged by Pals et al.,\textsuperscript{204} who have found that, unlike cocaine and desipramine, angiotensin does not influence the mechanism of catecholamine uptake by adrenergic fibers.

The cardiac effects of angiotensin are equally controversial. A positive inotropic action has been demonstrated in dogs in vivo\textsuperscript{244} and in normal and reserpinized cat papillary muscle in vitro.\textsuperscript{213} Downing and Sonnenblick\textsuperscript{27} have found that angiotensin had little or no direct effect on cardiac contractility. In fact, the decrease in coronary flow induced in some experiments by angiotensin brought about a negative inotropic effect. Other investigators state that the effects of angiotensin on the heart are multiple, though generally depressant, and are due to baroreceptor activation, with consequent depression of rate and force of contraction, and to coronary constriction and reduction in venous return.\textsuperscript{205} The conspicuous increase in left atrial and left ventricular diastolic pressures after beta-blockade indicate that beta-adrenergic activity is an important compensatory mechanism that enables the heart to maintain its output against a drastic increase in peripheral resistance. Adrenalectomy does not substantially diminish the cardiac and pressor responses to angiotensin.

Actually, the pressor effects of angiotensin are superficially similar to those of norepinephrine, though the former is quantitatively ten to 40 times more active in the resistance vessels.\textsuperscript{526} The diastolic pressure increase induced by angiotensin and the degree of baroreceptor activation and consequent bradycardia are more marked than those induced by norepinephrine. In this prevalence of alpha-adrenergic stimulant effects, angiotensin resembles methoxamine, although the vasoconstrictor effects of angiotensin appear to be more selectively pronounced in the splanchic area, particularly the kidney, while muscle and skin flow are correspondingly increased.\textsuperscript{345, 255}

Ross and White\textsuperscript{244} studied the effects of angiotensin in cats and found that intravenous doses of 0.1 $\mu$g/kg induced a biphasic pressor response characterized by a prompt pressure rise with a decrease in cardiac output and an increase in left atrial pressure, which was followed within 10 to 20 seconds by a slow decline of aortic pressure, an increase in aortic flow, ventricular dP/dt, and cardiac output. The administration of propranolol, a blocker of beta-adrenergic receptors, increased the arterial pressor responses, while left atrial pressure and left ventricular end-diastolic pressure rose and dP/dt fell. They also noticed an interesting dichotomy of response in venous flow, which was diminished in the inferior and increased in the superior vena cava. They attributed this difference to a differential effect
of angiotensin on splanchnic flow, as opposed to skeletal and cerebral blood flow.

Angiotensin has received extensive trial in the clinic. Like all other pressor drugs, it underwent an initial phase of enthusiasm followed by a persisting phase of sober reappraisal. Its limitations are as severe as those of methoxamine, with the added disadvantage that it is somewhat less reliable in cardiac failure or in sodium-depleted patients. It offers two theoretical advantages over norepinephrine: 1) its minimal effect on cardiac excitability; 2) the decreased danger of tissue necrosis upon accidental subcutaneous infusion. Its tendency to induce a maximal and sustained decrease in renal blood flow and the possibility of coronary vasoconstriction with larger doses constitute real disadvantages for the prolonged use of the drug, particularly in cardiogenic shock.

**PLV-2**

The synthetic octapeptide PLV-2 (2-phenylalanine 8-lysine vasopressin) is available only for clinical trial. It is of interest for two reasons: it may substitute for epinephrine with local infiltration anesthesia, and it can produce a usefully selective vasoconstriction during shock.

Its use as a vasoconstrictor for local anesthesia infiltration has been proposed because it produces fewer arrhythmias than epinephrine and it shows a highly selective postcapillary constriction. It should be noted that some arrhythmias have been observed with a combination of PLV-2 and halothane or cyclopropane in dogs. The postcapillary constriction retards outflow from the capillaries, which are the route of absorption of the local anesthetic agent. This is precisely what is needed. In addition, the loss of fluid from capillary to tissue, while disadvantageous as a systemic effect, is helpful in retarding absorption of a locally administered agent. In comparing the local constricting action of epinephrine and PLV-2, Klingenström and Westmark found that the latter produced no decrease in tissue oxygen tension, while epinephrine did. Using the hemostatic effect of PLV-2 vs. epinephrine as a criterion, good or very good vasoconstriction was noted in 80 per cent of the cases in which epinephrine was used, but in only 65 per cent of the cases with PLV-2.

In studies in shocked rats, PLV-2 produced better capillary perfusion and venous return than norepinephrine, angiotensin, and saline solution. This suggests that it may be possible to synthesize more selective pressor agents. If so, it would be particularly desirable to make postarterial perfusion more pressure-dependent than it now is. What is really needed is an agent that reduces the capacitance bed without shutting off the flow in any vascular bed.

PLV-2 has also decreased vascular reactivity to epinephrine and has sustained vasomotion and venular tone in rats during shock. The agent significantly improved survival rate, while norepinephrine and angiotensin failed to. In another study from the same laboratories, isoproterenol and PLV-2 produced essentially the same survival rates in rats. Combining the two drugs moderately increased survival. The relative contribution of circulatory vs. noncirculatory phenomena to the increased survival obtained with PLV-2 is unknown. It is known that reticuloendothelial phagocytic activity is greater after therapy with PLV-2 than with the other agents, in both normal and shocked rats.

The systemic effects of PLV-2 would seem to be a disadvantage. In normal dogs, Maxwell noted decreases in cardiac output, heart rate, coronary blood flow, myocardial minute oxygen consumption, and cardiac efficiency. Systemic, pulmonary, and coronary vascular resistance increased. Mean arterial pressure increased only 10 torr. In one series, three of ten patients infiltrated with PLV-2 suffered hypertension, and one of them developed severe bradycardia. The coronary vasoconstricting action of PLV-2 is of particular concern. It is possible that all polypeptides, particularly those related to vasopressin, possess this action.

Cohn et al. noted a surprising effect of PLV-2 in patients with hypotension or decompensated hepatic cirrhosis. In small doses, the agent produced renal vasodilation, and in larger doses, preferential extrarenal vasoconstriction resulting in redistribution of blood flow to the kidney. In general, however, there
were decreases in cardiac output with both doses.

Another analog of vasopressin, N-ω-triglycyl-
oxotocin, has been used in dogs in hemorrhagic shock.39 Compared with untreated controls, this agent produced impressive results: contraction of the capacitance bed in skeletal muscle and higher muscle blood flow, higher cardiac output, marked and long-lasting decrease in splanchnic blood flow, absence of metabolic acidosis, and a smaller decrease in oxygen uptake. There was no mortality in the treated group as opposed to a 40 per cent mortality in the untreated group.

Still another vasopressin analog, ornithine-
S-vasopressin, has been used to provide vaso-
constriction during tonsillectomy and nasal surgery.10 It was claimed that no cardiovascular complications were seen in these 500 operations. Facial pallor was observed in some patients.

**ISOPROTERENOL**

Isoproterenol is the prototype of the beta-
adrenergic stimulating agent. Therefore, it produces increased myocardial strength, frequency of contraction, and ventricular arrhythmias; relaxation of smooth muscle, including arterioles, bronchioles, uterus, stomach, intestine, and bladder; hyperglycemia; release of free fatty acids; and central nervous system excitation. The agent is included in this review even though it is not a conventional pressor agent; its increasingly extensive and uncritical use requires some discussion.

In a recent review,26 we suggested that isoproterenol could act as a transmitter substance. This statement provoked enough discussion that we thought it important to examine the question in more detail in the present review. We shall discuss some reasons for questioning acetylcholine or norepinephrine as the neurotransmitter mediating vasodilation and the difficulties of accepting isoproterenol as the mediator. Many questions could be answered by assuming that isoproterenol is released from certain sympathetic nerve terminals. For example, how do agents such as mephenetermine, methamphetamine, and ephedrine produce significant vasodilation if they allegedly act by releasing norepinephrine, an agent with very little vascular beta-stimulating action? Why should the sympathetic nerve endings in the blood vessels be virtually singled out for the privilege of releasing acetylcholine, a parasympathetic mediator?

Although it is true that acetylcholine can dilate systemic arterioles, proof that it is the sympathetic vasodilating transmitter is far from satisfactory. Most of the evidence is based on pharmacologic studies. Acetylcholine can dilate systemic arterioles. Atropine blocks the vasodilation produced by sympathetic stimulation.52 However, the amounts of atropine used are also sufficient to block sympathetic ganglia, where acetylcholine is unequivocally the transmitter. Evidence against acetylcholine as the mediator includes the dissimilar time courses of recovery of sympathetic vasodilation and vagal bradycaridia.191 Furthermore, intramuscular nerve-nerve synapses may exist,291 and these have not been studied as to their role in sympathetic transmission.

Norepinephrine does not have the necessary vasodilating properties to account for the vasodilation often seen with sympathetic stimulation, although some of its metabolites do. The breakdown of norepinephrine is not sufficiently rapid to account for the onset of vasodilation, however.

Failure of reserpine to abolish sympathetic vasodilation has been regarded as important supporting evidence that the mediator is not adrenergic.227,296 However, reserpine is more effective in depleting norepinephrine than its methylated congener, epinephrine. In sympathetic ganglia, more than half the epinephrine originally present remains after reserpine treatment.297 In view of the importance of the ethanolamine substituent, it is impossible to predict how isoproterenol stores would be affected by reserpine if such stores were to exist. This uncertainty is compounded by the fact that the mechanisms of uptake and storage of exogenous isoproterenol and norepinephrine are quite different.62 It is known, however, that the isoproterenol taken up by the isolated rabbit heart after reserpine pretreatment is capable of restoring the adrenergic response of the heart to tyramine or to acetylcholine.256

In dogs, beta-adrenergic blocking agents, such as propranolol and methoxamine, block sympathetic vasodilation.62 This is only cir-
cumstancial evidence in favor of isoproterenol, however. The most important prerequisite for proof is still lacking: no report of naturally occurring isoproterenol has yet been confirmed or denied. The main problems involve technical difficulties in isolation and in chemical identification. Methods in current use are close to "noise level" for detecting resting levels of epinephrine in blood and tissue. Therefore, isoproterenol, which is effective in many systems at approximately 1/10 the dose of epinephrine, might have escaped detection.

The effects of isoproterenol on the heart (positive inotropy and chronotropy) and blood vessels (arteriolar dilatation) would be expected to produce effects on the intact circulation unique among sympathimimetic amines. Such is the case. A major systemic action of isoproterenol is a striking increase in cardiac output in both dogs and man. This occurs not only because heart rate increases, but also because stroke volume is independently maintained or augmented. In addition, systemic vascular resistance decreases. The net result of increased inotropy and cardiac output and decreased systemic vascular resistance is that systolic arterial pressure often increases but diastolic pressure decreases out of proportion, with a resultant decrease or no change in mean arterial pressure. The decrease in systemic vascular resistance could contribute to the maintenance of stroke volume by facilitating runoff of blood, permitting a smaller end-systolic volume and a larger stroke volume. Both end-systolic and end-diastolic volumes decrease. This, according to Laplace's principle, increases the efficiency of contraction. In the human heart, the times of both ejection and total systole decrease.

The effect of isoproterenol on veins is controversial. In contrast to the opposing actions of alpha- and beta-adrenergic receptors in the arterial bed, stimulation of either of these receptors may produce venoconstriction. In the dog heart-lung preparation, were able to demonstrate that isoproterenol resulted in a decrease in systemic vascular blood volume, similar to that observed with the alpha-receptor stimulating agents phenylephrine and norepinephrine. By using appropriate adrenergic blocking agents, they demonstrated that the systemic venous bed contains both beta- and alpha-adrenergic receptors, and that stimulation of either produced venous constriction. On the other hand, Alexander found that, while norepinephrine and epinephrine constrict systemic veins, isoproterenol dilated them. Studies of the dog suggest that isoproterenol actively dilates pulmonary lobar arteries and small lobar veins. No active responses of larger pulmonary veins near the venoatrial junction was detected.

Part of the confusion concerning the effect of isoproterenol on veins arises from different initial experimental conditions, dosages and types of veins. With low doses, either no reaction or venodilation is observed. The venodilating effect is more marked when the initial tone of the venous segment previously has been increased by norepinephrine or by electrical stimulation, and is abolished by beta-adrenergic receptor blocking agents. High doses of isoproterenol, in strip preparations, result in venoconstriction, which can be inhibited by phentolamine, indicating an alpha-adrenergic receptor stimulating effect of these high concentrations. Isoproterenol, norepinephrine, and epinephrine have positive inotropic effects in preparations of inferior vena cava, superior vena cava, and pulmonary vein in the rat. These preparations respond like atrial or ventricular muscles to electrical stimulation and to a variety of drugs.

The response of a venous strip to isoproterenol seems to depend on the type of vein from which it is removed. Epinephrine and norepinephrine strongly contract strips from posterior caval and inferior mesenteric but not external jugular veins. Isoproterenol, in concentrations of 10^{-5} to 10^{-9} g/ml, relaxes inferior mesenteric but contracts posterior caval strips. In higher concentrations of 10^{-5} g/ml, it contracts both types of strips. Rice et al. produced venoconstriction with acetylcholine, norepinephrine, and sympathetic nerve
stimulation in cephalic and lateral saphenous venous preparations, but not in external iliac or splanchic veins. They concluded that the presence of valves plus a large amount of smooth muscle was necessary for venous constriction to occur.

Isoproterenol, then, produces effects qualitatively opposite to those of methoxamine—an agent which we have described as hazardous—but we are just as cautious about isoproterenol as about methoxamine. The reasons for this should be made clear by the following discussion.

Historically, the rationale for the use of isoproterenol in shock is sound. Several years ago, the dangerous effects of vasoconstricting drugs in shock became apparent. Using the concept that flow, rather than pressure, is the important variable for survival, a few investigators boldly suggested the use of vasodilators in a syndrome in which arterial pressure was already precariously low. However, many physicians were apprehensive about administering a vasodilating drug without also strengthening the heart. This apprehension was heightened when it became apparent that cardiac function was depressed even during “noncardiogenic” shock. It was then proposed that a vasodilator plus a positive inotropic agent be administered. Since vasodilation had been mediated by alpha-blocking agents, norepinephrine might be added to phenoxybenzamine, achieving the purpose of sustaining the heart and decreasing peripheral resistance, promoting a maximal increase in flow. Very few studies of this combination were performed, however, partly because the action of phenoxybenzamine outlasts that of norepinephrine by 48 hours to five minutes. Furthermore, norepinephrine cannot be administered until the alpha block of phenoxybenzamine has been firmly established—usually 40 to 60 minutes after the beginning of treatment. The next step seemed obvious; why not use the same drug to produce positive inotropy plus vasodilation? The logical choice was isoproterenol. The fallacy of this reasoning was that beta-stimulation was substituted for alpha-blockade to produce vasodilation, and these are not the same.

Experimental evidence of the potential value of isoproterenol in the therapy of shock is well established. Dedichen and Schenk observed an increase in coronary and vertebral artery flow in open-chest dogs after administration of isoproterenol, in spite of a decrease in arterial pressure. In dogs, the effectiveness of isoproterenol persisted during severe, acute, lactic acidosis, whereas the response to norepinephrine was attenuated. Severe hypoxia did not obtund the vasodilating response to isoproterenol. In dogs in which shock was produced by coronary microembolism, metabolic studies aimed at assessing adequacy of coronary blood flow during isoproterenol infusion suggested improved overall myocardial oxygenation, but did not exclude the possibility of continuing or regional myocardial ischemia. Isoproterenol increased heart rate and stroke volume, and therefore cardiac output during acute cardiac tamponade, in dogs, whereas norepinephrine failed.

When isoproterenol was administered to chick embryos, it protected them against ordinarily lethal doses of Escherichia coli endotoxin. Survival has been increased by therapy with isoproterenol during experiments with dogs in which shock was induced by hemorrhage, by injection of bacterial endotoxin, by acute coronary embolization, and in experiments in rats after hemorrhage, or temporary occlusion of the superior mesenteric artery. These were occasionally circumstances in which phenoxybenzamine was unsuccessful.

Studies of patients in shock also confirmed that during therapy with isoproterenol, myocardial function and cardiac output are temporarily improved. In 24 patients in whom shock had persisted in spite of correction of biochemical abnormalities and volume deficits, isoproterenol succeeded in increasing arterial pressure, cardiac output, and stroke volume and decreasing central venous pressure.

However, an initial enthusiasm and subsequent disillusionment, reminiscent of the pattern seen with norepinephrine, has occurred with isoproterenol. The amount of disillusionment with drugs seems to be proportional to the initial enthusiasm. The implication that the seemingly beneficial hemodynamic actions of isoproterenol effectively reverse clinical shock and improve survival is as yet unproven.
USE AND MISUSE OF PRESSOR AGENTS

In one study of 22 patients in hemorrhagic, traumatic, or septic shock, isoproterenol produced satisfactory responses only in those patients in whom previously administered dextan had produced no beneficial effect. In another study of 22 patients, isoproterenol was superior to dopamine in only three patients in whom the latter failed to increase cardiac output, whereas dopamine was superior in seven patients. Either amine produced an adequate response in four patients; both were required in two patients; and neither was effective in six patients. Nine patients were given isoproterenol on the first postoperative day after open-heart surgery and cardiopulmonary bypass in the hope of improving the hemodynamic status. Isoproterenol did not increase cardiac index, heart rate, and coronary blood flow. Myocardial oxygen demand was so greatly increased, however, that seven of nine patients developed decreased lactate consumption or increased lactate production, indicating anaerobic metabolism. Death, often sudden, has appeared after an initial “satisfactory” period in the treatment of patients in cardiac shock with isoproterenol. The factors described below could be working insidiously in patients not monitored with the same degree of sophistication possible in animal experiments. A closer look at experimental evidence reveals that in endotoxin shock in animals isoproterenol produces an initial improvement in hemodynamic status, but deterioration soon sets in, with an unremarkable long-term survival.

The discrepancy between experimental and clinical observations is in part due to important differences in the physiologic status of experimental subjects and patients. Although cardiac output may be greatly increased after therapy with isoproterenol, metabolic acidosis is not necessarily reversed, and signs of shock such as oliguria may remain unaltered. This is true particularly in patients in whom shock occurs as a complication of myocardial infarction or bacterial infection.

The complex effects that account for the underlying diseases also modify the response to isoproterenol. For example, in patients with coronary artery obstruction, the increase in cardiac output which follows administration of isoproterenol may provoke anginal pain and increase myocardial production of lactate. These are signs of acute myocardial ischemia. The inotropic effects of isoproterenol are such that myocardial oxygen demand is substantially increased, but the greater oxygen need may not be met by a corresponding increase in coronary blood flow.

There may be other causes for the failures of isoproterenol. As mentioned above, vasodilation from beta-adrenergic stimulation is not equivalent to that from alpha-adrenergic block. Alpha receptors exist in several vascular beds, including those of skin, mucosa, skeletal muscle, brain, lung, abdominal viscera, salivary glands and kidneys. Vascular beta receptors, on the other hand, occur in abdominal viscera and in skeletal muscle, predominantly the latter. Thus, the increase in cardiac output seen with isoproterenol may in fact be attributable mainly to increased skeletal muscle flow, and therefore be wasted, acting effectively as a shunt. Vasodilation produced by alpha block is passive, that produced by beta stimulation, active. Perhaps isoproterenol dilates vessels far more than is necessary or desirable. Cerebral and coronary vessels probably react very little to either alpha or beta stimulation. Therefore, if perfusion of either is borderline, lowering of arterial pressure may lower perfusion further, even though a comforting increase in cardiac output can be measured.

Another potential problem with isoproterenol resides in its ability to produce the type of myocardial lesions mentioned in the discussion of norepinephrine. These lesions resemble closely the lesions seen in human coronary artery disease or those produced by prolonged hypoxia. Cytochemical and histologic studies related to unmasking of intracellular phospholipid and to disturbances of electron-transport systems may reveal severe complications long before any histologic abnormality is apparent. In turtle hearts the necroses are located in a region where coronary supply is lacking, supporting the opinion that the necrotizing action of isoproterenol is not caused solely by vascular mechanisms.

Certain MAO inhibitors decrease the area of cardiac necrosis, possibly by decreasing the high myocardial oxygen requirement induced by isoproterenol. Bajusz and Jasmin have proposed that this protective effect is
mediated by liberated serotonin, which causes coronary vasodilation. The picture is confused, however, by the fact that not all MAO inhibitors protect against isoproterenol-induced lesions. The lesions produced by isoproterenol can also be modified by complex interactions with other catecholamines,207 with mineralocorticoids,209 with electrolytes,229 and with hemorrhagic shock.152

Beta-adrenergic blocking agents can antagonize the lesions competitively when administered prophylactically.24 However, when therapy is instituted four hours after administration of isoproterenol, no protection is obtained. The mechanism for the protection may be explained by the results of another study. Beta-block during hemorrhagic hypotension in dogs actually increases the systolic phase of coronary flow without changing cardiac output or systolic arterial pressure.112 Thus, an extravascular factor corrected by beta-block must impede coronary blood flow. This factor may be an exaggeration of the normal myocardial impedance to coronary blood flow in systole caused by myocardial contraction.350 Thus, this exaggeration results from the intense positive inotropic effect of increased endogenous sympathetic amines in hemorrhagic hypotension. This factor would alter the gradient through the transmyocardial arteries which perpendicularly perfuse the myocardium and supply the subendocardial plexus. When perfusion pressure is critically low, increased myocardial wall impedance to blood flow through the subendocardium might well result in subendocardial ischemia, necrosis, and hemorrhage. Isoproterenol would be expected to worsen this situation.

The decreased diastolic filling period arising from tachycardia plus decreased diastolic arterial pressure could also contribute to insufficient coronary perfusion. The latter is particularly important, since most of coronary blood flow occurs during diastole.

When coronary blood flow was decreased to about 40 per cent of control values in the non-working (isolated) heart,23 administration of isoproterenol was accompanied by markedly decreased chronotropic and inotropic responses. In some hearts, myocardial function actually was impaired.

When left ventricular heart failure was produced in dogs by ligating coronary vessels, isoproterenol led to a gradient between the left ventricle and aorta: this gradient would contribute to the pressure work of the heart and hence, oxygen consumption.205 These effects were accompanied by biochemical evidence of an increasingly inadequate cardiac output in proportion to the tissue oxygen demand and resultant progressive metabolic acidosis.

In dogs subject to hemorrhagic shock, mild to moderate intestinal hemorrhage and distention were noted in animals treated with isoproterenol, but not in those treated with nylidrin, a potent vasodilating agent.

It is not surprising that failure of isoproterenol to improve urinary output in man during shock has been reported.165 Even in normal animals 65, 241 or in man, infusion of isoproterenol may not change renal blood flow. Thus, the percentage of cardiac output distributed to the kidneys decreases. During experimental hemorrhagic shock, renal blood flow and splanchnic blood flow do not change,124 and following acute myocardial injury,250 renal blood flow actually may decrease with large doses of isoproterenol.

Other alarming but expected "side-effects" of isoproterenol have been observed, the most dramatic being tachycardia and arrhythmias. Tachycardia above a certain rate can decrease filling time to such a degree that cardiac output actually decreases. Whether the critical heart rate is elevated in the presence of the positive inotropic effects of isoproterenol is not known. Arrhythmias present a special problem, since they are often a cause of discontinuation of therapy. It has been suggested that the administration of potassium can decrease the incidence of arrhythmias without decreasing the positive inotropic effect of isoproterenol. Isoproterenol does have a less arrhythmogenic propensity than epinephrine. Perhaps this difference is due to the different effects on arterial pressure—abruptly increasing arterial pressure predisposes to arrhythmias; decreasing arterial pressure protects against arrhythmias.

**Dopamine**

Dopamine is the immediate precursor of norepinephrine in the biosynthetic pathways.
occurring in the sympathetic nerve endings.\textsuperscript{6}
Like norepinephrine, it has a striking positive inotropic effect, but, unlike norepinephrine it has very little vasoconstricting action. In fact, vasodilation can occur in some vascular beds, particularly renal.

The positive inotropic effect of dopamine is a beta-adrenergic effect, blocked by propranolol.\textsuperscript{212} However, the mechanism of this beta effect is in doubt. Dopamine could act directly. Blockade by propranolol does not exclude a direct action, since propranolol could block a direct effect of dopamine on beta-adrenergic receptors. As a second possibility, dopamine may act as a false transmitter, that is, substitute itself for norepinephrine at adrenergic nerve terminals and be released instead of norepinephrine (See the discussion of metaraminol). In fact, there is evidence that dopamine is a \textit{bona fide} transmitter in the caudate and lentiform nuclei of the dog.\textsuperscript{211} Finally, dopamine could have an indirect action, releasing catecholamines. The response to dopamine is decreased by reserpine and increased by cocaine.\textsuperscript{112} However, if dopamine is a false transmitter, then changes after cocaine do not necessarily imply an indirect effect, and, as we have seen earlier, failure to respond after pretreatment with reserpine does not imply indirect action.

The effects of dopamine on blood vessels are variable. Ross and Brown\textsuperscript{243} reported that in the cat dopamine caused dilation in the vascular beds of the left gastric, superior mesenteric arteries, and constriction in the vascular beds supplied by the hepatic and splenic arteries. Renal vasodilation was slight and inconsistent. McNay and Goldberg\textsuperscript{265} have also reported a mild vasodilating effect in the femoral bed. Dopamine caused an increase in coronary blood flow in dogs.\textsuperscript{23} The fact that this increase was proportional to the increase in myocardial oxygen consumption indicates that the induced coronary vasodilation was secondary to increased myocardial oxygen demands, rather than to a direct effect of dopamine.

The mechanism of the vasoconstricting action of dopamine is reasonably clear, since it can be prevented by alpha-adrenergic blocking agents.\textsuperscript{260} However, the dilating effects remain a puzzle. The effects are not mediated by beta-adrenergic receptors, since propranolol has no effect on them. Two other explanations for the vasodilating properties of dopamine have been advanced. One of the metabolic end-products of dopamine, tetrahydropapaveroline (THP), is structurally similar to papaverine and has similar vasodilating properties.\textsuperscript{157, 158} However, THP apparently causes vasodilation by a beta-adrenergic mechanism. The failure of propranolol to alter the vasodilating properties of dopamine\textsuperscript{262} rules out THP as a mediator. Furthermore, the amounts produced from dopamine are considerably less than those required to produce a depressor response.\textsuperscript{172} Brody \textit{et al.}\textsuperscript{51} have proposed that in the innervated hindquarter limb preparation, the dilation is reflex and is mediated by the neurogenic release of histamine. This hypothesis is strengthened by the fact that the dilation can be blocked by antihistaminic agents.\textsuperscript{51}

Most investigators have observed striking renal vasodilation following administration of dopamine.\textsuperscript{146, 147, 202, 261, 264, 265, 267} This is probably a direct effect.\textsuperscript{264} The almost specific renal vasodilation is the unique property of the agent. Isoproterenol and dopamine are the only catecholamines which do not decrease renal blood flow, and only dopamine can consistently increase it. According to one report, most catecholamines produce renal ischemia, which is blocked by alpha-adrenergic blocking drugs.\textsuperscript{244}

Accompanying the dopamine-induced renal vasodilation is a significant improvement in renal function: increases in urinary output, sodium, potassium, and osmolar excretion, clearances of para-aminohippurate and inulin, and extraction of para-aminohippurate. These changes may or may not be dependent on the increase in renal blood flow.

The systemic hemodynamic effects of dopamine are as predicted. In sheep, there is an increase in cardiac output, a decrease in systemic vascular resistance, and no change in arterial pressure.\textsuperscript{171} In the dog, Black and Rolet\textsuperscript{26} also noted a positive inotropic effect without a change in arterial pressure. They attributed the maintenance of arterial pressure to the balancing of alpha- and beta-adrenergic stimulating effects, although, as discussed above, the vasodilation of dopamine is not
mediated by beta-adrenergic receptors. Also in dogs, its inotropic effect decreases ventricular end-diastolic pressure simultaneously with an increase in cardiac output. There is little associated increase in heart rate or irritability when small doses are infused.237

These potentially useful properties of dopamine seem to carry over into pathologic states. In dogs in hemorrhagic shock, dopamine increased mean arterial pressure and cardiac output and decreased systemic vascular resistance. Systemic vascular resistance was not increased when dopamine was administered during traumatic shock. During cardiogenic shock produced by intracoronary injections of microspheres, dopamine increased both cardiac output and coronary flow. Interestingly enough, most of these phenomena were abolished by propranolol.66

In the few comparative studies reported, dopamine has a slight edge over isoproterenol. In dogs during hemorrhagic shock,124 dopamine decreased heart rate, while slightly increasing mean arterial pressure. Cardiac output, as well as splanchic and renal blood flows, increased. Isoproterenol, in contrast, decreased mean arterial pressure, increased heart rate, and did not significantly change splanchic or renal flows. In dogs following coronary artery occlusion with microspheres, dopamine increased cardiac output and renal blood flow.57,256 Isoproterenol increased renal blood flow at smaller doses only. Dopamine was more effective in increasing mean arterial pressure, while increasing cardiac work. The author noted that the arrhythmogenic properties of dopamine did not appear to restrict its use, as they did the use of isoproterenol.

Reports on the use of dopamine in patients are few, but these are encouraging. In one patient with a traumatic aorticopulmonary fistula complicated by postoperative low cardiac output, dopamine infusions restored cardiac output and renal output.216 Both dopamine and isoproterenol were administered to 22 patients suffering from various types of severe shock.389 The response and the ultimate success depended on the initial status of the patient. Dopamine was particularly successful in comparison with isoproterenol in patients with normal or low systemic vascular resistance. The authors suggested that not only should the hemodynamic status of each patient be assessed before therapy, but that the responses to different therapies should be evaluated before the decision is made.

It appears that dopamine has several features which make it attractive for clinical use. In addition to its positive inotropic effect, renal vasodilating effect and slight chronotropic effect, its onset of action is rapid, and it is quickly metabolized. It is, in essence, more gentle than isoproterenol. As with any drug, more extensive clinical investigation is necessary to uncover unanticipated and undesirable side-effects, as well as to establish a significant reduction in mortality. However, it seems that dopamine would be useful in treating patients in shock in whom cessation of renal function appears to be life-threatening.

GLUCAGON

Glucagon is a polypeptide hormone produced by the alpha cells of the pancreas. Glucagon's primary site of action is the liver, where it acts by stimulating the formation of cyclic adenosine monophosphate (3',5' AMP) from ADP and by activating phosphorylase, the enzyme which catalyzes phosphorylolytic cleavage of 1,4 linkages in glycogen to yield glucose-1-phosphate.263 Porcine glucagon, extracted from the pancreas, has been used to treat hypoglycemia.209

In 1950, Farah and Tuttle,114 reported that glucagon increased cardiac output in the canine heart-lung preparation. The positive inotropic and chronotropic effects of glucagon have been established in intact dogs, and canine papillary muscle,114,139,245 as well as in cat papillary muscle,139,139 the rat and guinea pig isolated hearts,114 and the human heart.210,309,420 The mechanism of this response is unknown. It appears that the beta-adrenergic blocking agent, propranolol,215,245 blocks the chronotropic but not the inotropic effects, while pretreatment with reserpine blocks neither.245 The prior administration of tyramine diminishes the positive inotropic effect.245 Theophylline blocks the inotropic action of glucagon but leaves the inotropic effect of calcium chloride unchanged.

The relation between cyclic AMP and positive inotropy has received considerable attention. Catecholamines activate the same enzy-
motic machinery as glucagon, and it has been shown that their inotropic action on the heart is concomitant to a parallel increase in myocardial cyclic AMP levels. The effect of glucagon on cyclic AMP levels in the heart is controversial, however. Two independent studies have demonstrated increased levels of cyclic AMP, while one study showed no change. Other work indicates that the inotropic effect of glucagon can be dissociated from net changes in cyclic AMP. Furthermore, propranolol blocks the inotropic actions of catecholamines and their ability to increase cyclic AMP levels, but does not interfere with the inotropic effects of glucagon. This has induced Parmley et al. to postulate that the mechanisms of catecholamines and glucagon may be quite different, and that the effects of the latter may be completely independent of their action on cyclic AMP. The actions of glucagon on the heart may be more complex than hitherto supposed. It has been found recently that glucagon activates adenylyl cyclase and increases the cyclic AMP contents of cat and human heart particles both before and after propranolol, suggesting that there are at least two receptor sites in myocardial tissue responsible for activation of this enzyme. One of these sites may be intracellular and connected with the molecular mechanism of contraction (relaxing factor). The inotropic response of glucagon is qualitatively different from catecholamine-induced inotropism; glucagon does not decrease the time to peak tension, while epinephrine does.

Glucagon may also have vasodilating properties. Katz et al. using catheter and cuff electromagnetic flowmeters in dogs, measured the effect of glucagon on arterial flow. Glucagon (1, 5 or 25 µg/kg) injected intravenously increased flow in mesenteric and renal arteries, and in the ascending and descending aorta. In the carotid and femoral vessels the response was biphasic: an initial increase followed by a decrease. Intra-arterial injection of glucagon through the tip of the catheter flowmeter increased flow in all vessels, but the sensitivity to glucagon varied markedly. The order of decreasing sensitivity was: mesenteric, renal, carotid, femoral.

The hemodynamic effects of glucagon in normal man are superior to those of most available pressor agents. Cardiac output is usually augmented, the increases ranging from 19 to 30 per cent. Stroke volume may be enhanced, or unchanged. The effects on cardiac outputs of individual patients are variable, and the presence of heart disease may alter the response to glucagon. Variable effects on systemic arterial pressure have been observed. Mean arterial pressure may increase moderately or remain unchanged. Systemic vascular resistance remains unchanged or is reduced. Parmley et al. reported an increase in stroke work and no change in mean rate of left ventricular ejection, while Williams et al. observed an increase in the mean rate of ejection without a significant change in stroke work. The maximum rate of rise of left ventricular pressure increased, while end-diastolic pressure remained constant or decreased, suggesting a positive inotropic effect.

It appears that glucagon possesses many of the characteristics of the ideal pressor agent for the treatment of certain types of shock, namely: 1) its ability to increase force and rate of shortening and tension development of the myocardial fiber (positive chronotropism and inotropism) with a concomitant increase in blood flow through some critical vascular beds without any increase in systemic resistance; 2) the prompt onset of action (2–3 min) and the rapid termination of effects (15–30 min); 3) the absence of tachyphylaxis in intact animals, although tachyphylaxis has been reported in the canine heart–lung preparation; 4) the lack of arrhythmic propensities, giving it a definite advantage over inotropic catecholamines; 5) the ability to induce a response even in the face of total beta-adrenergic blockade or previous catecholamine depletion; 6) the ability to increase A-V conduction (positive dromotropic effect) without the precipitation of arrhythmias in patients treated with propranolol.

In dogs after crushing of the SA node, glucagon produced a marked and sustained increase in the rate of A-V nodal discharge.

For these reasons, glucagon has been tried in several clinical situations: in heart failure, cardiogenic shock, patients whose removal from cardiopulmonary bypass has been difficult, and in the immediate postoperative pe-
period following prosthetic valve replacement. Glucagon has also been tried in the pharmacologic diagnosis of pheochromocytoma. The test is based on its ability to release endogenous catecholamines. Sheps and Maher claim to have obtained by this means a greater number of positive results than with histamine, though their evidence does not appear convincing.

As may be anticipated, the use of a potent hormone is fraught with serious problems. The amounts of drug used to produce a positive inotropic effect have ranged from one to 150 times the amounts needed to raise blood sugar in man, hence they are often well above the physiologic range (0.5 \( \gamma \)/kg vs. 0.5–75 \( \gamma \)/kg). Glucagon secretion, calcium metabolism, and parathyroid function appear to be interdependent. Glucagon manifests in man striking hypocalcemic effects, which are particularly pronounced in hypercalcemic patients. Avioli recently has added evidence that, in addition to promoting hypercalcemia, glucagon lowers blood calcium by stimulating release of the calcium-lowering peptide calcitonin. Much of this calcium passes into the urine; some calcium may be transported elsewhere. Perhaps glucagon increases myocardial intra- or extracellular calcium ion concentration, offering an explanation for the positive inotropic action. One also wonders about the consequences of simultaneous glucagon administration and massive transfusions with blood containing sodium citrate. The latter chelates calcium ion and could add to the problem.

Since glucagon is a peptide, it must be administered parenterally, an inconvenience in long-term therapy. Other “side-effects” of glucagon are its saluretic properties and its tendency to produce intestinal atony, nausea, vomiting, immunologic reactions, and catecholamine release. Nausea and vomiting are particularly serious, having been observed in all reports and noted in as many as 88 per cent of patients receiving the drug intravenously. These side-effects, combined with the fact that the positive inotropic effects of glucagon are either weak or nonexistent in patients with heart disease, suggest caution and a more thorough study before its acceptance in the clinic. The effort may be worthwhile to the anesthetist, since glucagon can reverse halothane-induced myocardial depression without the danger of arrhythmias.

Some Clinical Applications of Pressor Agents

Spinal and Epidural Anesthesia

Probably the most common use of vasopressors in anesthetic practice is to counteract the hypotension seen during spinal or epidural analgesia. The special case of hypotension during obstetrical regional anesthesia is discussed in the following section. As with obstetrical anesthesia, the first decision is whether to administer vasopressors prophylactically. This practice should probably be avoided since: 1) not all patients will need vasopressors; 2) vasopressor therapy can be instituted rapidly when needed; 3) the possibility of inadvertent hypertension exists; and 4) as discussed extensively elsewhere, these agents have deleterious effects of their own. An intravenous infusion should be in place, of course, and a vasopressor ready to administer. Position change and fluid administration should be tried first, unless the pressure is falling rapidly. It is probable that elevating the legs is more effective than placing the patient in a Trendelenburg position. Elevating the legs can return as much as 700 ml into the circulation. There is no evidence that the Trendelenburg position can increase cerebral blood flow, and some evidence to the contrary. In fact, this position actually may be harmful during shock in rats.

Once a decision to use a pressor agent is made, it seems logical to select one which antagonizes the circulatory derangements induced by spinal anesthesia. These malfunctions are discussed in great detail in Greene’s classic monograph on spinal anesthesia, and need not be repeated in detail here. In essence, spinal anesthesia induces hypotension, bradycardia, decreased cardiac output, and arteriolar and venous dilatation. Recent evidence presented by Shimozato and Etten suggests that hypotension induced by spinal analgesia may arise primarily from increased vascular distensibility of capacitance vessels, and secondarily from decreased resistivity to pre- and postcapillary resistance vessels in the anes-

82
N. T. SMITH AND A. N. CORBASCIO
Anesthesiology
July 1970
thetized area. Ephedrine, although not an ideal agent, appears to be the best one available to antagonize the effects of spinal anesthesia.

Unfortunately, little information about the clinical role of vasopressors in treating hypotension from spinal anesthesia is available. Fortunately, most of this information is of good quality. Methoxamine, theoretically, is a poor choice to reverse the hypotension of spinal anesthesia. Indeed, Li and co-workers noted that high spinal anesthesia almost invariably decreased cardiac output. In three of seven subjects subsequently receiving methoxamine, cardiac output was reduced further. Moreover, some of the patients in the series had virtually total sympathetic blocks. Braunwald and his co-workers showed that in human subjects whose cardiac sympathetic tone had been abolished, the responses of the heart to increased peripheral resistance or increased venous return essentially obey Starling's law. Intravenous infusion of methoxamine produces a consistent increase in left ventricular volume during all phases of the cardiac cycle in conscious human subjects (in other words, acute cardiac dilation). It is probable that when resistance to ventricular outflow is increased by methoxamine, the left ventricle, in order to develop a higher systolic pressure, is obliged to increase its size. This increase in dimensions, especially in diastolic volume, could also explain the increase in stroke index, and occasionally in cardiac index, noted with the drug. This is obviously an inefficient way to increase cardiac output. Furthermore, the total sympathetic block occurring during high spinal anesthesia, together with the use of methoxamine, may induce an even greater cardiac dilation than that observed with either alone.

Ward et al. after administration of spinal anesthesia to normal subjects, noted an early increase in systemic vascular resistance and decreases in cardiac output and initial ventricular impulse, each of which partially recovered by five minutes. Subsequent administration of methoxamine produced a large increase in systemic vascular resistance and a decrease in cardiac output. Ephedrine sufficient to produce twice as great a pressor response as methoxamine increased cardiac output and initial ventricular impulse, while causing only a modest and transient increase in systemic vascular resistance. A lowering of the heart rate seemed to be the predominant factor with methoxamine, while an increase in stroke volume occurred with ephedrine.

**Obstetrics**

In few situations is the anesthetist faced with the dilemma that arises when a woman in labor becomes hypotensive. Hypotension which produces little more than discomfort in a healthy young woman can be lethal to the fetus, yet attempts to elevate arterial pressure with vasopressors can be equally disastrous. When hemorrhagic hypotension occurs in the nonpregnant woman, uterine flow is among the first to shut down to preserve coronary and cerebral flow. This mechanism apparently is maintained during pregnancy, suggesting that, teleologically, maternal welfare is uppermost.

The exact level of hypotension needed to produce a decrease in uterine blood flow sufficient to lead to fetal distress is not precisely known, but evidence suggests that it ranges from 80 to 100 torr, systolic. Moya and Smith studied the effects of spinal hypotension on the fetus and the newborn in a group of infants of 590 women undergoing cesarean section. A decrease in maternal systolic arterial pressure to less than 100 torr doubled the incidence of depressed infants, as measured by the Apgar score. Duration of hypotension is just as important as degree.

Attempts to use vasopressors to treat this potentially hazardous hypotension have met with disappointing results, however, both in animals and man. These failures are partly due to the fact that the uterine vessels seem to have only alpha-adrenergic receptors, that is, they are capable of reacting to autonomic stimuli only by constricting. This makes sense, since in the normal state the uterine vessels are maximally dilated. However, it also means that any drug which stimulates both kinds of adrenergic receptors will produce uterine vessel constriction without any balancing beta-mediated dilation. Thus, the predominantly constrictor agents have produced the most untoward results. Using chronically
implanted flowmeters in pregnant ewes, Creiss and Crandell\textsuperscript{169} were able to measure the effects of vasopressor agents on uterine blood flow, fetal heart rate, and fetal blood pressure. Maternal hypotension was associated with slowing of fetal heart rate. Although the pressor agent phenylephrine restored the maternal blood pressure, the degree of fetal bradycardia increased.

Vasieka and associates\textsuperscript{401} found that restoration of maternal blood pressure by methoxamine failed to correct fetal bradycardia. In fact, the tetanic contractions and increased uterine tone produced by the agent were associated with fetal bradycardia. The degree of fetal distress (bradycardia) was more severe than that seen during comparable tetanic contractions caused by an overdose of oxytocin. On the basis of these observations, they concluded that the bradycardia was caused by: 1) compromise of uterine placental circulation subsequent to the pre-existing maternal hypotension; 2) uterine hyperactivity caused by vasopressors; 3) direct constricting action of methoxamine on fetal and placental circulation.

The tetanic tetany seen with methoxamine is interesting. It is well known that beta-adrenergic stimulation depresses uterine contractility (see the discussion of epinephrine). Barden and Stander\textsuperscript{22} recently have demonstrated that noradrenaline has a uterine stimulating action which is blocked by the alphadrenergic blocking agent phentolamine. Thus, methoxamine and phenylephrine may produce undesirable alpha-mediated uterine hyperactivity.

The fetal hypoxic response (bradycardia) to vasopressors is exacerbated when these drugs are used to treat maternal hypovolemic hypotension. By using a special animal preparation, Romney and co-workers\textsuperscript{528} were able to measure simultaneously maternal blood pressure, uterine blood flow, and fetal heart rate, as well as the oxygen tension of the fetus, the uterine tissue, and the arterial blood of the mother before and during hemorrhage and following treatment with methoxamine or with transfusion. Transfusion of blood restored all maternal and fetal measurements to normal levels. Methoxamine made matters worse for the mother and fetus, despite an increase in maternal blood pressure. Boba and associates,\textsuperscript{29, 40, 318} also developed a special animal preparation which permitted measurement of maternal and fetal blood pressure, pulse, and oxygen tension, without disturbing the fetus\textit{in utero}. They found that graded hemorrhage produced fetal bradycardia which was associated with fetal hypoxia. Although the administration of phenylephrine restored maternal blood pressure, it caused further declines in fetal heart rate and arterial pressure. Their finding that fetal bradycardia and fetal hypoxia proceeded\textit{pari passu} seems to confirm the belief that fetal bradycardia is an expression of fetal distress.

The bradycardia associated with fetal distress is probably not the cause of the distress, since the administration of atropine during prenatal hemorrhage in dogs abolished the fetal bradycardia, but did not change the rate of progressive fetal hypoxia.\textsuperscript{318} The same phenomenon was seen when phenylephrine and atropine were used to correct maternal hypotension, that is, fetal bradycardia disappeared, but hypoxia remained.\textsuperscript{40}

Slindor and his colleagues have begun a systematic evaluation of vasopressors in pregnant ewes. Hypotension produced by spinal anesthesia led to fetal hypoxia, acidosis and hypercarbia. As might be anticipated, methoxamine produced further deterioration, accentuating these derangements.\textsuperscript{269} Ephedrine, although it did not correct the situation totally, at least did not produce further deterioration, and often actually improved fetal status.\textsuperscript{261} Metaraminol, with a pharmacologic action lying between those of methoxamine and ephedrine, but with predominant vasoconstricting properties, had intermediate effects on hypotension—fetal status was not improved but did not deteriorate.\textsuperscript{262}

As for the administration of vasopressors before spinal or epidural anesthesia, one is confronted with a variety of opinions ranging from pleas for routine use\textsuperscript{122} to just as emphatic condemnation.\textsuperscript{31} One has to adopt one or the other of these polarized attitudes, since it is difficult to predict which patient is liable to suffer dangerous hypotension. We feel that prophylactic administration is not indicated, for the following reasons: 1) When the alternatives are properly used, vasopressors are rarely needed. 2) Maternal hypotension of
USE AND MISUSE OF PRESSOR AGENTS

less than 100 torr, systolic, can still occur in spite of prophylactic vasopressor administration. In one series, this phenomenon was observed in 23 per cent of 1,100 patients.\textsuperscript{291} 3) The danger of interaction of oxytocic or ergot derivatives is real (see below). This interaction can produce severe hypertension and cerebral vascular accidents. 4) Hypertensive reactions from vasopressors themselves are common.

Death or permanent motor and mental disability can be the fate of the infant as the result of severe maternal hypotension. The incidence of the latter is unknown, but it is probably greater than we suspect. Several alternatives are open to the anesthetist before he considers vasopressor therapy. However, since duration as well as degree of hypotension is important, the initiation and evaluation of these alternatives must begin as soon as systolic arterial pressure falls below 100 torr and be completed within six to eight minutes. The first alternative is to place the patient on her side. If this is not possible, the uterus can be displaced to the left side, either manually or by tilting the table. The latter maneuver proved effective in 93 per cent of 106 patients who developed hypotension after spinal anesthesia.\textsuperscript{205}

Compression of the veins of both legs by application of elastic bandages should be carried out as a prophylactic measure when it is especially dangerous for the mother to develop hypotension. It is also indicated as a therapeutic measure in patients with severe hypotension unresponsive to position change, fluids, or uterine displacement. Since as much as 1,000 ml of blood may be pooled in the legs\textsuperscript{16} and since venous obstruction from the heavy uterus and lithotomy position may impair venous return, compression of the veins will force most of this blood back into the general circulation. This procedure should be carried out \textit{after} compression of the inferior vena cava is relieved. Otherwise, the blood is forced into the pelvis and may increase venous pressure sufficiently to produce placental separation. To provide maximum benefit this procedure should be done within two to three minutes of onset of hypotension.

If not given prophylactically, a rapid intravenous infusion of 300 to 500 ml of lactated Ringer's or physiologic saline solution should be administered immediately after deciding that position change and uterine displacement are ineffective. By using only an 18-gauge intravenous needle, it can be administered within five minutes. Like vasopressors, fluids increase maternal arterial pressure, but unlike vasoconstrictors, they also increase uterine blood flow.\textsuperscript{160} Admittedly, the oxygen-carrying capacity of the blood is diminished by diluting it with fluids. However, the doubling of uterine blood flow seen\textsuperscript{160} probably more than compensates for the smaller decrease in oxygen content.

Finally, if the above measures fail, one has to resort to vasopressors. If the mother develops signs of cerebral, medullary, or coronary ischemia, vasopressors should be administered immediately, and uterine blood flow given secondary consideration. The choice of an agent must be based on animal studies, but results thus far coincide with predictions based on a knowledge of their pharmacologic properties. Methoxamine, phenylephrine, angiotensin, norepinephrine and metaraminol should be avoided. Of the theoretically “safe” vasopressors—methamphetamine, mephenetermine and ephedrine—only ephedrine has been tested; it was found to be more useful than the constrictors agents listed above. Fifteen- to 25-mg increments of ephedrine given intravenously should suffice. However, it should be borne in mind that the very properties which allow ephedrine to increase pressure and uterine blood flow simultaneously—its beta-adrenergic properties—also may delay the course of labor by inducing uterine inertia. Ironically, this uterine relaxation may contribute to the improved flow, just as the tetany produced by methoxamine may interfere with flow.

Several cases of severe persistent maternal hypertension following the combined obstetric use of an oxytocic and vasopressors have been reported.\textsuperscript{67, 145, 275} Some of these patients have suffered rupture of a cerebral vessel, with hemiplegia and other serious neurologic sequelae. In most of these cases, methoxamine had been given as a prophylactic or therapeutic measure, followed by injection of either ergonovine or methylergonovine. Some patients received both ergot preparations
and pituitrin, as well as a vasoconstrictor. The interval between the administration of the constrictor and oxytocin was occasionally as long as two or three hours.

Several factors probably contribute to this hypertension. 1) Vasoconstriction could persist even after several hours. We have noted a marked pressor response when atropine was given 90 minutes after the injection of mephentermine, even though arterial pressure had returned almost to normal (Smith, N. Ty, unpublished data). 2) Ergot derivatives and oxytocics have constricting effects of their own. 3) Contraction of the uterus produced by oxytocics pushes a large bolus of blood into the general circulation, with consequent increases in cardiac output and arterial pressure. 4) Delivery of the placenta removes a large shunt, increasing systemic vascular resistance. 5) The sympathetic block of spinal or epidural anesthesia is often diminishing at the time of delivery of the placenta.

Prevention of hypertension is better than treatment. Ergot derivatives or pituitrin should never be given following vasoconstrictor therapy, which means that pressor agents should be avoided, if possible. If immediate reduction of arterial pressure is necessary, amyl nitrite is the best drug. The effect is temporary, however, and other measures should be rapidly instituted. Trimethaphan given as an infusion or chlorpromazine given in increments of 2–5 mg every 30 to 60 seconds is an appropriate measure.

**Cardiogenic Shock**

The rationale for treating cardiogenic shock with vasoressors seems to be more sound than those for using them to treat any other conditions. First, during cardiogenic shock there is apparently a positive feedback loop which should be broken by increasing arterial pressure. The simultaneous effects of a weakened heart, pain, anxiety, and reflexes contribute to decreased arterial pressure. The reduced arterial pressure leads to further decreases in coronary perfusion, in myocardial strength, and again in arterial pressure and coronary perfusion. Second, although certain areas of the myocardium are lost, a significant surrounding ischemic area with low perfusion might be salvaged. The arterioles in this border area are probably maximally dilated, and therefore, coronary perfusion is pressure-dependent. Myocardial oxygen uptake, in turn, is perfusion-dependent. Third, increased strength in the viable portions of the myocardium is needed to compensate for decreased strength in the ischemic regions.

It is proper to examine how valid this hypothesis is: increasing arterial pressure will reverse cardiogenic shock. About 80 per cent of reported cases in which cardiogenic shock has been treated with vasoressors showed increases in arterial pressure. In those studies in which cardiac output was measured, the success rate in raising this variable was somewhat less, around 60 per cent. Norepinephrine and metaraminol increased cardiac output more consistently than methoxamine and angiotensin.

The most important consideration in this lethal syndrome, cardiogenic shock, is survival. We have examined 29 reports containing at least some mortality figures to evaluate the efficacy of vasoressors in cardiogenic shock. Minimal criteria were used to judge these studies: 1) The paper had to define shock. Assuming a definition was given, the variations encountered were amazing, extending from a systolic blood pressure lower than 90 torr lasting a few minutes to a systolic pressure lower than 60 torr for a two- to three-hour period with unresponsiveness to oxygen or morphine therapy, plus signs of shock, such as cold, pale skin and oliguria. 2) The study had to be prospective, not retrospective. 3) The study had to have acceptable and well-matched controls, not controls from another group of patients treated at another hospital, drawn from a different population of age and sex, exposed to different nursing care and ancillary therapy, and evaluated by different criteria for shock and for therapy; certainly not “controls” from last year’s records. These three criteria are the least possible in good conscience. Several other criteria were omitted: statistical evaluation, a description of the method for measuring arterial pressure, and an account of the duration of shock.

Of the 29 studies surveyed, 14 claimed success with vasoressors, that is, the agents lowered mortality from some kind of “control.”
Twelve showed no success, that is, vasopressors either did not improve mortality or actually increased it. Three studies were so confusing for the authors that it was impossible to determine the results. Of the 14 studies showing decreased mortality, none satisfied our modest criteria. Of the 12 studies noting no success with vasopressors, three satisfied these criteria. Therefore, after 15 years of vasopressor therapy for cardiogenic shock, we must admit that vasopressors cannot be proved successful, and they may even be detrimental. Even by generously allowing the validity of all of the studies, vasopressors would manage to decrease mortality by only about 20 per cent, from 50 to 60 per cent. At best, vasopressor therapy is disappointing. At worst, it is worthless or even dangerous. Arterial pressure is elevated by vasopressors, but patients die anyway. Therefore, there is something wrong with the hypothesis that perfusing the coronary arteries will reverse cardiogenic shock.

Why have vasopressors been so disappointing in cardiogenic shock? There are several possible explanations: 1) We may be using the wrong agents. 2) We may be using the right agents in the wrong way. 3) We may be using the right agents in the wrong patients. 4) We may be using a different population as a control. 5) We may be using the wrong approach altogether. Each of these items will be discussed briefly.

1) The wrong agents are being used. Although increased arterial pressure can increase coronary perfusion and myocardial oxygen availability, it can also increase myocardial work and minute oxygen consumption. In addition, those vasopressors which increase the rate of myocardial fiber contraction can also increase myocardial oxygen consumption without elevating arterial pressure. The oxygen-wasting effect of norepinephrine in normal animals has been shown. As mentioned above, norepinephrine can produce experimental heart failure with or without areas of myocardial necrosis resembling small myocardial infarcts. Against these oxygen-wasting effects is balanced the increasing efficiency of a heart operating from a smaller end-diastolic volume, assuming a vasopressor with positive inotropic properties is given. Which of these factors is dominant in the ischemic heart is not known. Inotropic vasopressors may also precipitate arrhythmias in an already irritable heart, thus contributing to mortality in patients who might otherwise have survived.

2) We may have been using the right agents in the wrong way. First, there is a tendency to raise arterial pressure too high during cardiogenic shock. Eighty to ninety torr systolic pressure should be sufficient to perfuse coronary arteries. If systolic pressure is elevated above 90–100 torr, any increase in cardiac output is usually lost. Second, vasopressors are often administered too long. Metaraminol and norepinephrine both produce tachyphylaxis, metaraminol probably from the release and depletion of norepinephrine, and norepinephrine itself from decreased plasma volume. Norepinephrine tachyphylaxis, produced by significant postcapillary constriction, can be treated with plasma infusion. Many patients in cardiogenic shock have been treated successfully with plasma infusion after failure with vasopressors.

3) It is possible that we have been using the right agents in the wrong patients. Vasopressors seem to be used rather indiscriminately in all patients with cardiogenic shock. Not all patients in cardiogenic shock show the expected reflex increase in total peripheral resistance which accompanies a decrease in arterial pressure. The etiology of the lack of response is interesting. It is probably due to a baroreceptor and chemoreceptor response initiated in the ventricles and coronary arteries. We might expect vasopressors to be more useful in patients with normal peripheral resistance than in those with existing excesses of vasoconstriction, but there is no agreement about which group might be more successfully treated with vasopressors.

4) The effects of vasopressors have been evaluated using different populations of patients and controls. In the last 15 years most patients in cardiogenic shock have received vasopressors. Therefore, the controls cited in most reports were obtained at least 15 years ago. Many patients are saved today by more advanced nursing care, monitoring, and more
rapid cardiopulmonary resuscitation. These patients are now added to the population being studied, and may actually increase the number of bad risks in the series, thereby weighting the series unfavorably.

5) The pharmacologic approach itself may be wrong. There may be a large segment of patients in whom no drug will help the severely damaged myocardium. In these, perhaps only mechanical means, such as counterpulsation, will help.374

In summary, there are good theoretical indications for the use of vasopressors in cardiogenic shock. There is no doubt that they have saved many patients who might otherwise have died. However, many also have died who might otherwise have lived. Whether these two factors balance each other is still in question. Perhaps the pharmacologic approach itself is wrong.

References


USE AND MISUSE OF PRESSOR AGENTS


N. T. SMITH, AND A. N. CORBASCIO


USE AND MISUSE OF PRESSOR AGENTS


241. Livesay, W. B., and Chapman, D. W.: The treatment of acute hypotensive states with


271. Mills, J. L., and Moran, N. C.: Cardiac contractile force response to ephedrine and other sympathomimetic amines in dogs


336. Robinson, R. L.: Stimulation of the catecholamine output of the isolated, perfused


