CIRCULATORY EFFECTS OF VASOACTIVE DRUGS IN CURRENT USE FOR TREATMENT OF SHOCK*

A RECLASSIFICATION BASED ON EXPERIMENTAL AND CLINICAL STUDY OF THEIR SELECTIVE ARTERIAL AND VENOUS EFFECTS

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INTRODUCTION

FOR almost a decade we have searched for better understanding of the role of vasopressor agents in altering regional and systemic blood flow. Except in instances in which adequacy of perfusion pressure is a critical factor, it is questionable whether elevation of arterial pressure at the expense of added arteriolar constriction favors improvement in blood flow.

The hemodynamic effects of epinephrine and norepinephrine have been extensively studied. Three primary sites of action are recognized: 1) a cardiac action relating to rate, rhythm, and inotropic effects, which may result in improved myocardial contractility and improved cardiac output; 2) a constrictor action on arterioles (the resistance vessels), which results in increase in arterial pressure; and 3) an effect on the venules and veins (the capacitance vessels), which results in either mobilization or pooling of blood.

The venous capacitance bed, as the term implies, serves two functions. It provides venous channels for return of blood from capillaries to the heart, and it serves as a reservoir in which blood may be pooled or from which blood may be mobilized for "active" circulation. Remarkably little is presently known about the effects of various vasoactive drugs on venous capacitance. Since the venous bed contains between
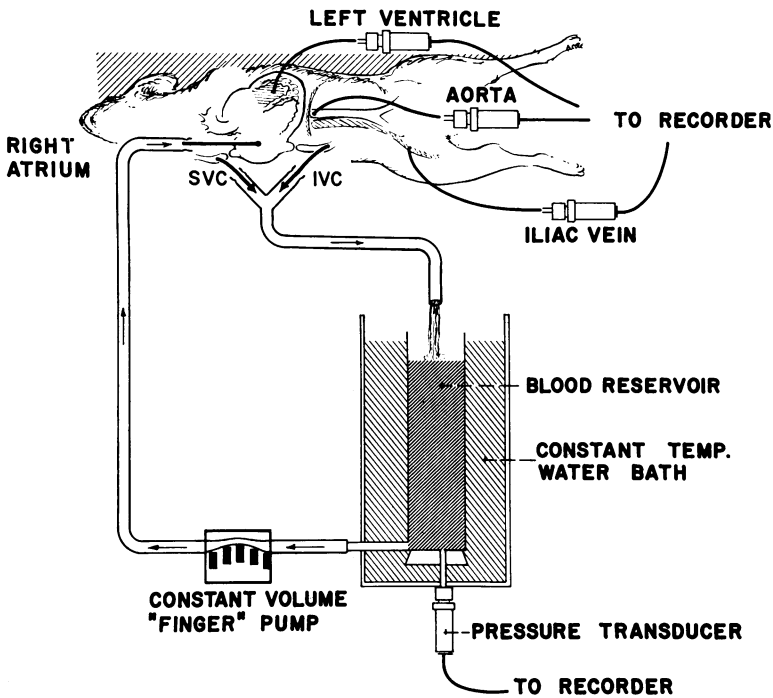
Fig. 1. System for measurement of venous return and related hemodynamic studies.

75 and 80 per cent of the total blood volume, this portion of the circuit is quantitatively very important in the distribution of intra-vascular volume.

In a series of studies on dogs, we sought to differentiate between the effects of vasopressor agents on the resistance and the capacitance vessels. We then planned additional studies in human patients in shock in order to pinpoint the specific action of various so-called vasopressor amines and obtain a more rational basis for the clinical use of various vasoactive drugs for the treatment of circulatory shock.

EXPERIMENTAL STUDIES

Our initial experiments were done collaboratively with Dr. C. Lewis in a series of 45 dogs anesthetized with pentobarbital.[1] Atropine was administered to minimize changes in rhythm due to carotid sinus re-flexes. Blood was passively drained from the superior vena cava and the inferior vena cava into a reservoir 30 cm. below atrial level (Figure 1). This technique was previously used by Drs. MacLean,

TABLE I—EFFECTS OF VASOACTIVE DRUGS ON MEAN ARTERIAL
PRESSURE, HEART RATE, AND VENOUS RETURN

Drug	No. of dogs	Mean arterial pressure mm. Hg Control	Test	Heart rate beats/min. Control	Test	p	Change in venous return ml.	p
Isoproterenol	20	106	70	136	185	<0.001	+109	<0.001
Mephentermine	41	93	91	136	167	<0.001	+ 82	<0.001
Levarterenol	34	93	138	145	164	<0.001	+ 34	NS
Metaraminol	37	88	132	139	151	<0.01	+ 3	NS
Epinephrine	35	95	131	151	165	<0.001	− 21	NS
Angiotensin	36	91	124	143	141	NS	− 51	<0.001
Phenylephrine	37	88	147	149	137	<0.05	− 74	<0.001
Methoxamine	32	88	119	146	140	NS	− 79	<0.001

NS = not significant

Visscher, Spink, and Weil[2] when venous return was measured during
a study of the mechanism of endotoxin shock in dogs. Changes in
volume of blood in the reservoir reflected changes in venous return.
The volume was continuously recorded by electronic technique. Blood
was returned from the reservoir to the right atrium at a constant rate
and in amounts that provided essentially normal cardiac output, em-
ploying a Sigmamotor finger pump. The reservoir system had been
primed with 6 per cent dextran solution or blood from a donor dog.
Under these experimental conditions, cardiac output was kept constant,
and the arterial pressure, measured in the aorta at the level of the
diaphragm, served as an indication of the effects on resistance vessels.
After bypass had been established, mean arterial pressure was approxi-
mately 50 mm. Hg less than during the control period. Then a vaso-
active drug was administered in amounts sufficient to restore arterial
pressure to the approximate value observed during the control period.
The effects on venous return that accompanied this elevation in arterial
pressure were measured. Changes in mean arterial pressure, heart rate,
and venous return that followed administration of the various vaso-
active drugs are shown in Table I.

    Observations with mephentermine (Wyamine) were of special
interest. Mephentermine was actually *not a vasopressor drug* under
these experimental conditions. Although large amounts of mephenter-
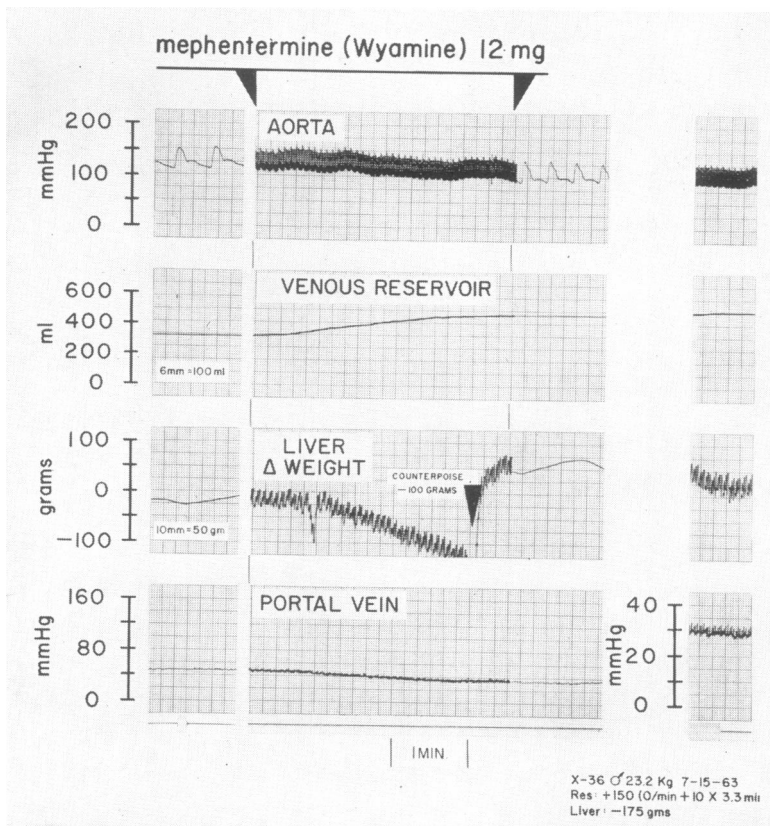mine were administered, the mean arterial pressure was slightly reduced

Fig. 2. A representative recording of changes in venous return, i.e., volume of venous reservoir, in relation to changes in aortic and portal vein pressures. Effects on the volume of blood contained in the liver reservoir are also shown.

rather than elevated. However, there was a highly significant increase in venous return (Figure 2). The aortic pulse pressure and left ventricular systolic pressure were often increased, but the aortic diastolic pressure fell. This accounted for the slight fall in mean arterial pressure.

The findings with isoproterenol (Isuprel) were very similar to those obtained with mephentermine. There was a greater decrease in the aortic pressure and, at the same time, a profound increase in venous return.

The effects of epinephrine, norepinephrine, and metaraminol were variable. After administration of these drugs, the pressor effect was accompanied by either an increase or a decrease in venous return, and both occurred with equal frequency.

TABLE II—CHANGES IN LIVER WEIGHT AND PORTAL VEIN PRESSURE
FOLLOWING ADMINISTRATION OF VASOACTIVE DRUGS, WITH
CARDIAC OUTPUT KEPT CONSTANT

Drug	No. of dogs	Change in liver weight g	Change in portal vein pressure mm. Hg
Isoproterenol	4	—19.4	—2.7
Mephentermine	7	—35.2	—1.6
Levarterenol	5	— 9.7	+0.2
Metaraminol	8	— 4.6	+0.6
Epinephrine	5	—11.9	+4.5
Angiotensin	9	— 8.7	+3.4
Phenylephrine	4	+33	+7
Methoxamine	6	+18	+3.9

As the arterial pressures were increased by administration of meth-
oxamine (Vasoxyl) and phenylephrine (Neo-Synephrine), the venous
return was reduced. The hypertensive effect of angiotensin (Hyper-
tensin), a nonadrenergic pressor agent, was also accompanied by a
decline in venous return.

To define the site of pooling, various organs were suspended on one
arm of an electronic balance with its blood supply intact, by use of a
technique described by MacLean, Weil, Spink, and Visscher (Figure
3). Alterations in volume of blood contained in these organs were
detected as acute changes in weight. After administration of the various
drugs, there were profound changes in venous return but no essential
change in weight of a suspended lung. These changes in pulmonary
blood volume did not account for the changes in venous return.

When changes in the weight of the liver were measured, however,
we were able to account for some change in venous return (Table II
and Figure 2). Following the administration of isoproterenol and meph-
entermine, there was a predictable increase in venous return and a
simultaneous decline in the liver weight. After phenylephrine and
methoxamine, a decrease in venous return was accompanied by an
increase in liver weight.

When liver weight was clearly reduced following administration
of one of these drugs, there was a concomitant decline in portal vein
pressure, and when liver weight clearly increased, portal venous pres-
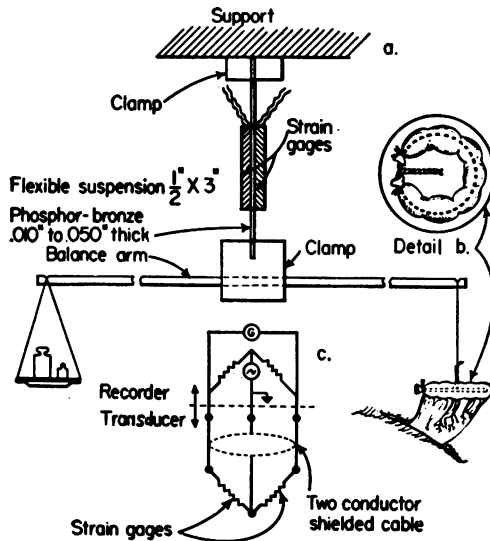sure was elevated. These changes in portal pressure, after administra-

Fig. 3. Diagrammatic representation of weighing device, including electrical circuit. (Reproduced with permission. *Proc. Soc. Exp. Biol. Med. 92*:602-605, 1965.)

tion of isoproterenol and mephentermine, indicated that blood is not "milked" out of the capacitance vessels of the liver by constriction of the portal veins. If this were the case, the reduction in hepatic volume would have been associated with an increase in portal venous pressure. To the contrary, the portal venous bed appeared to dilate. Mephentermine and isoproterenol decreased pooling by opening flood gates that controlled the volume of blood held in the hepatic reservoir. Methoxamine and phenylephrine, which increased rather than decreased the pressure in the portal venous bed, closed these flood gates and increased the volume of blood held in the hepatic reservoir. Indirect evidence implicates sphincteric contraction of the small efferent venules that conduct blood to the hepatic veins. No specific reservoir sites other than the liver have as yet been located.

To summarize, isoproterenol and mephentermine consistently increased venous return. The acute effects of levarterenol (Levophed), metaraminol (Aramine), and epinephrine (Adrenalin) were variable. Angiotensin, phenylephrine, and methoxamine clearly reduced venous return. The drugs that increased venous return tended to reduce portal vein pressure, and those that decreased venous return increased portal vein pressure. There is also a spectrum of effects with relation to heart

TABLE III—HEMODYNAMIC ACTIONS OF TWO DISCRETE GROUPS OF
VASOACTIVE AMINES

	Heart rate (myocardial contractility)	Venous return and cardiac output	Mean arterial pressure (and peripheral arterial resistance)	Venous pooling (liver)	Portal vein pressure ("flood gates")
Phenylephrine ⎫ † Methoxamine ⎭	decreased or unchanged	reduced	increased	increased	increased
Isoproterenol ⎫ * Mephentermine ⎭	increased	increased	reduced	reduced	reduced

† Alphamimetic
* Betamimetic

rate. The adrenergic drugs that reduced the size of the venous capacitance bed usually increased heart rate. Quite the opposite was the case with drugs acting primarily on the resistance bed. These tended to reduce the heart rate, at least in part because of baroreceptor reflexes. The hemodynamic actions are summarized in Table III.

Our study in dogs, therefore, demonstrated that in addition to recognized myocardial and arteriolar vasoconstrictor actions, vasopressor agents have important effects on the venous circuit. Angiotensin, methoxamine, and phenylephrine, which act predominantly on the resistance vessels, constrict arterioles. They also constrict small effervent venous vessels that act as flood gates, with consequent pooling of blood in the liver and elsewhere. This explains the reduction in venous return that accompanies their pressor action. To the contrary, mephentermine has no arteriolar constrictor action, but in addition to its myocardial action, it has a selective venous effect. It increases venous return presumably by vasodilation of efferent venules, consequently opening flood gates, and thereby reducing the volume of blood held in selected reservoirs.

CLINICAL OBSERVATIONS

Armed with this information we studied the hemodynamic effects of these same vasoactive drugs at the bedside of patients in circulatory stock. The methods of study and results have for the most part been reported elsewhere.

TABLE IV—HEMODYNAMIC DATA ON SEVEN PATIENTS TREATED WITH
MEPHENTERMINE

	Control	Mephentermine
Arterial pressure mm. Hg	85/50	86/52
Cardiac index l./min./M²	1.77	2.14
Heart rate beats/min.	93	103
Peripheral arterial resistance dynes sec. cm.⁻⁵	1772	1446

TABLE V—COMPARISON OF HEMODYNAMIC RESPONSE TO METARAMINOL
AND THE RESPONSE TO MEPHENTERMINE IN FOUR PATIENTS
WITH CIRCULATORY SHOCK

	Metaraminol	Mephentermine
Arterial pressure mm. Hg.	117/62	104/61
Cardiac index l./min./M²	1.42	1.59
Heart rate beat/min.	90	105

Mephentermine

In collaboration with Dr. Vasant Udhoji[3] the hemodynamic actions
of mephentermine were evaluated in nine patients with shock due to
causes other than volume deficits. Mephentermine increased cardiac
index (Table IV). Reminiscent of the lack of pressor actions in experi-
mental animals was the insignificant increase in arterial pressure and
heart rate as cardiac output was increased following administration of
this drug. Peripheral arterial resistance was therefore clearly decreased.
For this reason we would actually have to speak of mephentermine as
a "vasodilator" drug.

A comparison between the effects of metarminol and mephentermine
was made in four additional patients (Table V). Mephentermine evoked
a slightly higher cardiac index at a lower arterial pressure and hence a
lower resistance value than metaraminol. The heart rate was consistently
increased following the administration of this drug. In confirmation of
the concept developed from our observations in animals, the predom-
inant effect of mephentermine was on the myocardium and the capaci-
tance bed. Metaraminol had actions on both the capacitance and the
resistance circuits. The increase in arterial pressure was mainly the result

of constriction of the resistance vessels with lesser effect on cardiac output and more pronounced arterial pressor action.

Isoproterenol

Isoproterenol, an adrenergic drug with primary "vasodilator" activity, had beneficial hemodynamic actions in the experimental treatment of shock produced by endotoxin,[4] and in reported cases of shock of cardiac and bacterial causes in patients.[5] In our studies of hemodynamic effects in dogs, isoproterenol consistently increased venous return and decreased arterial resistance.

We subsequently explored the hemodynamic actions of isoproterenol in a group of 14 patients in whom shock was due to either bacterial infection, cardiac cause, or fluid loss unresponsive to volume repletion.[6] On infusion of approximately 5 μg. of isoproterenol per minute, cardiac output increased markedly, from an average of 1.6 to 3.2 l. per minute per meter of body surface square (l./min./M^2). This change was significant at the 2 per cent level ($p < 0.02$). Unlike normotensive human subjects, in whom arterial pressure almost always decreased after injection of isoproterenol, arterial blood pressure was increased by an average of 33 mm. Hg. Heart rate increased from 72 to 106 beats per minute, but even at this increased rate the volume ejected with each stroke was increased from an average of 31 to 49 ml. ($p < 0.02$). The central venous pressure was simultaneously lowered. This demonstrated that, in addition to effects on heart rate, isoproterenol improved myocardial competence and ventricular function since cardiac output was markedly increased at a time when filling pressure was reduced. A speed-up in dye circulation, an increase in the skin temperature of extremities, and an increase in urine flow were observed. These objective changes indicated improvement in systemic as well as in the regional blood flows.

Angiotensin

Clinical investigations previously reported by Udhoji and Weil[7] concerned the acute hemodynamic effects of angiotensin in patients who manifested circulatory shock. The effect of angiotensin was also compared to that of metaraminol and norepinephrine administered in doses that elicited comparable arterial pressor actions. The cardiac index was consistently less when arterial pressure was maintained at average

TABLE VI—HEMODYNAMIC ACTIONS OF PHENTOLAMINE DURING
CLINICAL SHOCK (15 TRIALS, 8 PATIENTS)

	Control	Phentolamine	p
Mean arterial pressure mm. Hg	73	59	<0.001
Cardiac index l./min./M²	2.8	3.6	<0.001

levels of between 70 and 80 mm. Hg with angiotensin, than it was when levarterenol and norepinephrine were infused with arterial pressure maintained at comparable levels. Cardiac output during infusion of angiotensin was 1.7 l./min./M², whereas it was 2.4 l./min./M² during infusion of norepinephrine and metaraminol. The differences were significant at the 1 per cent level ($p<0.01$).

These observations in patients again confirmed fundamental differences between the effects of two groups of drugs. Angiotensin, a non-adrenergic drug, acts primarily on the smooth muscle of the arteries and arterioles (resistance vessels). Metaraminol and levarterenol, in addition to their effect on resistance vessels, modify venous capacitance and myocardial contractility with a consequently greater increase in cardiac output.

Vasodilator Drugs

An incidental observation in animals was very helpful for clarifying the spectrum of effects of various vasoactive substances. In one of the experiments on venous return in the dog, Dr. C. Lewis, working then as a summer research fellow in our laboratory, injected phentolamine (Regitine), a sympatholytic drug, at the completion of a venous return experiment. To our surprise, as the arterial pressure fell, venous return increased rather than decreased. This effect was very similar to that observed with mephentermine and isoproterenol.

In subsequent studies in 13 patients, parallel effects of phentolamine were observed (Table VI). The effects were even more dramatic in five additional cases in which phentolamine was administered in conjunction with metaraminol. Metaraminol had been infused in amounts that would restore arterial pressure to "normal" values. After addition of phentolamine, cardiac index increased from 2.5 to 3.6 l./min./M². Only a slight decline in arterial pressure occurred, but pulse pressure
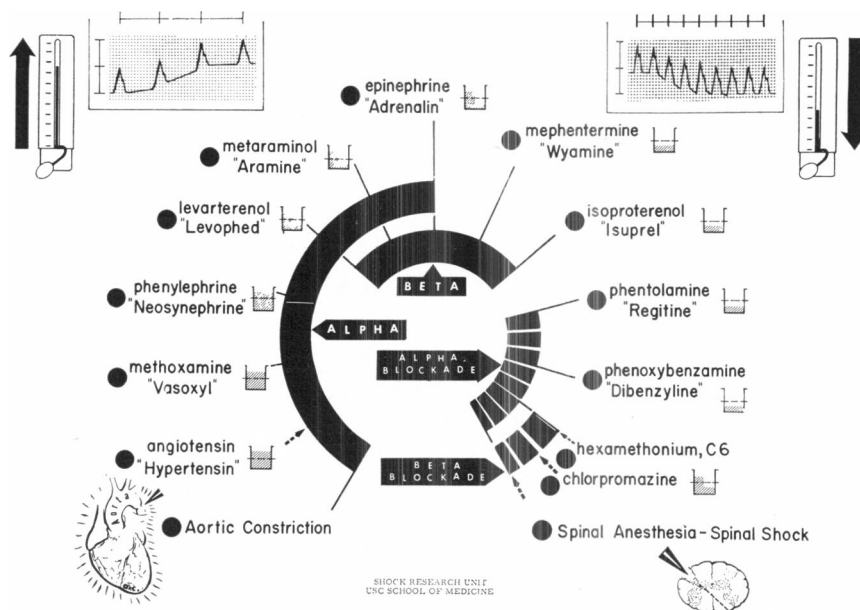
Fig. 4. Spectrum of hemodynamic actions of vasoactive drugs. (Reproduced with permission. *Calif. Med. 103*:310-320, November 1965.)

was more markedly increased because of a decline in diastolic pressure. Peripheral arterial resistance was reduced to 65 per cent of the initial value and there were objective signs of improved peripheral blood flow.

ALPHA- AND BETA-ADRENERGIC MODES

The terminology we use in our clinical unit to describe the hemodynamic actions observed in the experimental laboratory and at the bedside adopts in part the alpha- and beta-adrenergic concepts originally proposed by Ahlquist.[8] Although the intravascular receptors postulated by Ahlquist have not been anatomically demonstrated, drugs that act as if they block actions at these sites are described as either alpha- or beta-adrenergic receptor blocking agents.[9] We prefer a more general concept that describes *modes of cardiovascular action* in a pragmatic sense rather than in terms of more general pharmacological effects on specific receptor sites. This translates Ahlquist's concept into a practical outline that is useful to the clinician for predicting the hemodynamic responses of patients after administration of vasoactive drugs. The physician is really quite confused by seemingly paradoxical developments in this field, and a practical, useful classification is direly needed.

We refer to *alphamimetic* and *betamimetic* vasoactive drugs. The drugs that oppose these adrenergic hemodynamic actions are referred to as *alphalytic* and *betalytic* agents. Figure 4 summarizes our current concept of the relationships between "vasopressor" and "vasodilator" substances in terms of their alpha- and beta-adrenergic actions. Angiotensin, methoxamine, phenylephrine and, to a lesser extent, levarterenol, metaraminol, and epinephrine have primary effects on the resistance circuit. They increase arterial pressure and the volume of blood in the capacitance bed (shown by the beakers) and decreased heart rate and venous return. We define this as an alphamimetic action. Angiotensin is not an adrenergic (sympathomimetic) drug, either in terms of its molecular structure or its pharmacological characteristics. Its effects are not blocked by alphalytic phenoxybenzamine (Dibenzyline) nor by phentolamine. Yet, angiotensin is marketed for clinical use in competition with other "vasopressor" agents to restore blood pressure in treatment of acute hypotension and shock. Levarterenol, metaraminol, and epinephrine have mainly alphamimetic actions, but they also have a second action. They increase heart rate, reduce arterial pressure, and decrease the volume in the capacitance bed. This opposite action is described as a betamimetic effect.

Mephentermine and isoproterenol, relatively pure betamimetic drugs, have primary effects on the capacitance bed and on the heart. They decrease venous pooling, and increase venous return. At the same time they reduce arterial tonus and therefore act as "vasodilator" drugs.

Drugs that oppose the alpha-adrenergic agents, such as phenoxybenzamine and phentolamine, cause a decline in arterial blood pressure, increase in venous return, and increase in cardiac output. Their action, therefore, simulates in these respects the action of beta-adrenergic (betamimetic) drugs.

When an alpha-betamimetic pressor agent, such as levarterenol or metaraminol, is combined with an alphalytic drug such as phentolamine, the betamimetic action becomes dominant. These features have been clearly delineated, both experimentally in our laboratory and more recently in clinical studies reported by us.[10] Phentolamine, like levarterenol and metaraminol, is a short-acting drug, dissipated in minutes; but the action of phenoxybenzamine persists for 24 hours or longer. Since the effects of the combination depend on the dose of component drugs, adjustment of varying alpha and betamimetic actions is simplified

by use of short-acting phentolamine. The pharmacological effects of adding phentolamine to levarterenol (or phentolamine to metaraminol) include a cancellation of alphamimetic actions, leaving betamimetic actions comparable to those of isoproterenol predominant.

The spectrum is completed by reference to combined alpha and beta blockade. This follows administration of ganglionic blocking drugs, neural (spinal) block or transection of the spinal cord. On the extremes of the spectrum, the severe increase in resistance caused by large amounts of the alphamimetic effects simulates aortic constriction. The extreme condition of alpha-betalytic blockade simulates transection of the spinal cord.

Based on our experience in the Shock Research Unit, by far the predominant mechanism of shock due to causes other than fluid deficit and pump (cardiac) failure is a fault in the capacitance bed. Under these circumstances, the rationale for treatment with alphamimetic drugs, such as phenylephrine and methoxamine or even alpha-beta-mimetic drugs such as levarterenol and metaraminol, is increasingly more difficult to defend. The selective use of beta-adrenergic drugs such as mephentermine and isoproterenol, or their pharmacologic counterparts, alpha blockers such as phentolamine, provide a more promising and rational approach to therapy. However, the ultimate value for improving survival in patients is yet to be proved.

CONCLUSIONS

Vasopressor amines are widely used for treatment of acute hypotension and circulatory shock in an effort to restore "normal" or near-normal arterial pressure levels. Drugs that act primarily on the resistance circuit (alphamimetic action), such as levarterenol and metaraminol, and also phenylephrine and methoxamine, have been widely used to achieve pressor effects. Yet, circulatory shock is primarily defective blood flow rather than failure of perfusion pressure, and treatment is best directed to improvement of effective flow rather than arterial pressure. Such improvements in flow have been more consistently observed after the administration of drugs that act primarily on the capacitance vessels and the heart, such as phentolamine and isoproterenol. While these decrease arterial resistance, and often lower blood pressure, they consistently increase venous return and cardiac output and improve myocardial function.

The seeming paradox of "vasopressor" and "vasodilator" treatment of shock is partially resolved by demonstration of the differences in actions on resistance vessels (alphamimetic) and those that act primarily on capacitance vessels and the heart (betamimetic). Drugs, such as phentolamine, that block alphamimetic actions, simulate betamimetic agents in their hemodynamic actions. The routine use of alphamimetic drugs for treatment of shock is being abandoned. The betamimetic and alphalytic drugs are coming into use as more rational and possibly as more effective measures for treatment of the deficit in effective blood flow which is the actual cause of circulatory shock.

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