

REVIEW ARTICLE

CARDIOVASCULAR EFFECTS OF SOME COMMONLY USED PRESSOR AMINES

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I. INTRODUCTION

THE NUMBER of available sympathomimetic drugs has increased to such extent that selection of the best one for a particular situation has become difficult. This review primarily concerns the considerations involved in choosing the most suitable pressor drug to prevent or relieve hypotension generally encountered by anesthesiologists. These considerations are: (a) cardiac effects, (b) vascular effects, and (c) dependability.

Several recent articles,¹⁻⁴ textbooks⁵⁻⁸ and monographs⁹⁻¹¹ summarize the pharmacology of sympathomimetic drugs. Table 1 is a compilation of 26 drugs available commercially with their synonyms and chemical structures, as well as the extent of their clinical usefulness as pressor agents, nasal decongestants, smooth muscle relaxants and central nervous system stimulants. The ten pressor agents discussed in this article will be: epinephrine, levarterenol, metaraminol, phenylephrine, hydroxyamphetamine, methoxamine, ephedrine, methamphetamine, mephentermine and methyldaminoheptane.

II. COMPARISON OF CARDIAC EFFECTS

The cardiac effects of sympathomimetic amines, exemplified by epinephrine, consists of stimulation of all properties of the heart including automaticity, excitability and contractility. This pattern simulates the response of the heart to sympathetic nervous excitation but does not characterize all other sympathomimetic drugs. Indirect cardiac effects of epinephrine may be expected as a result of the accompanying vascular reactions. Reflex cardiac slowing can antagonize the tachycardia, and vasoconstriction may interfere with ventricular emptying, as well as alter venous

return to the heart. The outcome of these indirect actions, as well as the local stimulation of the heart, is assessed by measurement of heart rate, rhythm, contractility, output and metabolism. Each of these measurements will be discussed to emphasize that the ten pressor agents under discussion have dissimilar cardiac effects.

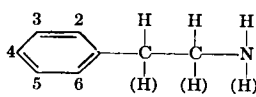
(A) *Heart Rate and Rhythm.* Pressor drugs can be grouped into three classes depending upon the predominance of one of the following actions: increase in activity of sino-auricular node and ventricular foci; decrease in activity of sino-auricular node predominantly due to reflex action, and depression of ventricular foci.

(1) INCREASED ACTIVITY OF SINO-AURICULAR NODE AND VENTRICULAR FOCI: Epinephrine, levarterenol, ephedrine, hydroxyamphetamine, metaraminol, methamphetamine and methyldaminoheptane are capable of producing sino-auricular tachycardia and ventricular arrhythmias (table 2). The sino-auricular tachycardia is preceded usually by a brief period of bradycardia. The latter is a reflex mechanism because it is almost completely eliminated by atropinization. The details of this mechanism will be discussed under the next class of drugs.

The explanation for the sino-auricular tachycardia cannot be obtained from studies in human subjects. Perfusion of the isolated heart and studies in the denervated heart *in situ* show that epinephrine and all the drugs in this class can cause sino-auricular tachycardia. One can assume that sino-auricular tachycardia in man arises from a local action on the cardiac pacemaker.

The initiation of ventricular extrasystoles and tachycardia by epinephrine has been demonstrated by many techniques: in human subjects with ventricles arrested by carotid sinus pressure or with auriculo-ventricular block;¹² in dogs anesthetized either with cy-

TABLE 1
LIST OF AVAILABLE SYMPATHOMIMETIC DRUGS WITH CORRESPONDING CLINICAL USES

Official Names* (Trade Names)	Chemical Structure					Major Clinical Uses				
						P = Pressor R = Relaxant N = Nasal Decongestant C = Central Nervous System Stimulant				
Epinephrine USP (Suprarenin)	3-OH	4-OH	OH	CH ₃		P	R			
Levarterenol USP (Levophed)	3-OH	4-OH	OH			P				
Isoproterenol USP (Isuprel)	3-OH	4-OH	OH	C ₃ H ₇			R			
Metaraminol NND (Aramine)	3-OH		OH	CH ₃		P		N		
Phenylephrine USP (Neosynephrine)	3-OH		OH	CH ₃		P		N		
Hydroxyamphetamine USP (Paredrine)		4-OH		CH ₃		P		N		
Nylidrin NND (Arlidin)		4-OH	OH	CH ₃	C ₁₀ H ₁₃		R			
Methoxamine USP (Vasoxyl)	2-CH ₃ O	5-CH ₃ O	OH	CH ₃		P		N		
Methoxyphenamine NND (Orthoxine)	3-CH ₃ O			CH ₃	CH ₃		R			
Isopropenamine (Compound 20025)	2-Cl		OH		C ₃ H ₇		R			
Ephedrine USP			OH	CH ₃	CH ₃	P	R	N	C	
Pseudoephedrine (Sudafed)			OH	CH ₃	CH ₃		R	N	N	
Phenylpropanolamine NND (Propadrine)			OH	CH ₃				N	C	
Amphetamine USP (Benzedrine)				CH ₃				N	C	
Dextroamphetamine USP (Dexedrine)				CH ₃					C	
Methamphetamine USP (Methedrine)				CH ₃	CH ₃	P		N	C	
Mephentermine USP (Wyamine)				(CH ₃) ₂	CH ₃	P		N	C	
Phenylpropylmethylamine NND (Vonedrine)			CH ₃		CH ₃			N		
Methylaminoheptane (Oenethyl)	n-butyl			CH ₃		P		N		
Tuaminoheptane NF (Tuamine)	n-butyl			CH ₃				N		
Methylhexanamine NND (Forthane)	i-butyl			CH ₃				N		
Isometheptene NND (Octin)	i-pentenyl			CH ₃	CH ₃		R			
Cyclopentamine NND (Clopene)	Cyclopentyl			CH ₃	CH ₃			N		
Propylhexedrine USP (Benzedrex)	Cyclohexyl			CH ₃	CH ₃			N		
Naphazoline NF (Privine)	2-(Naphthylmethyl)imidazoline							N		
Tetrahydrozoline NND (Tyzine)	2-(Tetrahydro-naphthyl)imidazoline							N		

* USP = United States Pharmacopeia XIV (1955); NF = National Formulary X (1955); NND = New and Nonofficial Drugs 1957.

clopropane¹³⁻¹⁵ or chloroform,^{16, 17} and in excised papillary muscle of the cat's heart.^{18, 19} Information for other pressor agents is either incomplete or not uniform. Ephedrine and hydroxyamphetamine induce ventricular arrhythmia in man¹² but only the former is active in the dog.¹³ Levarterenol consistently induces ventricular arrhythmia in the dog¹³⁻¹⁵ but the effects in man are variable.^{20, 21} Price²² noted that infusion of levarterenol (9 to 12 μ g./minute) produced ventricular extrasystoles in one of 10 conscious subjects, in 5 of 6 subjects anesthetized with cyclopropane, in 2 of 4 anesthetized with Fluothane, but in none of 5 anesthetized with ether. It appears

that although levarterenol is not as consistent as epinephrine in the production of ventricular extrasystoles, levarterenol is not free from this hazard.

The uncertainty as to the role of pressor agents other than epinephrine is probably associated with the lack of definition of the basic mechanisms involved in the induction of arrhythmia. There is reason to suspect that unlike sino-audicular tachycardia, ventricular tachycardia is not entirely a local cardiac phenomenon but is dependent upon the accompanying pressor response.²³⁻²⁶ Resolution of mechanisms of initiation of arrhythmia should lead to clarification of drug effects.

TABLE 2
COMPARATIVE EFFECTS ON CARDIAC RATE AND RHYTHM

Sympathomimetic Drugs	Sino-Auricular Rate*	Ventricular Rate Arrested Heart†	Ventricular Arrhythmia Cyclopropane (Dog)‡	References
Epinephrine	Increased and Decreased ↓	Increased	Induced	12-16, 38
Levarterenol		Unaffected or Increased	Induced	13-15, 20, 22, 38
Ephedrine		Increased	Not Induced	12, 13
Hydroxyamphetamine		Increased	Induced	13, 14, 39-41
Methamphetamine			Induced	13-15, 34
Metaraminol				42, 43
Methylaminoheptane			Induced	15
Methoxamine	Decreased Only ↓	Unaffected	Not Induced or Prevented	15, 29, 33, 34, 38
Phenylephrine		Unaffected or Increased	Not Induced	12, 13, 15, 20, 28
Mephentermine	Increased and Decreased		Prevented or Induced	38, 44-46

* The rate changes are based on electrocardiographic observations in man and animals.

† Ventricular activity is arrested by carotid sinus pressure or accompanies auriculoventricular block by disease process.

‡ Ventricular extrasystoles following intravenous injection of amine in a dog under cyclopropane anesthesia.

(2) SINO-AURICULAR BRADYCARDIA ACCOMPANIED BY UNCERTAIN EFFECTS ON VENTRICULAR FOCI: Methoxamine and phenylephrine are unique pressor agents because they do not induce sino-auricular tachycardia either in the intact or isolated heart. In the latter, neither drug alters heart rate²⁷ but in the former a pressor response is usually accompanied by bradycardia particularly in human subjects.^{28, 29} The difference in behavior of the isolated and intact heart suggests that the bradycardia is a reflex mechanism. A rise in blood pressure is known to activate pressoreceptors in the carotid sinuses and aortic arch, to increase cardiac vagal tone and to inhibit sympathetic tone. The reflex increase in vagal tone is the predominant reflex action because atropinization in man³⁰ and cervical vagotomy in dogs³¹ significantly reduce the intensity of cardiac slowing initiated by methoxamine and phenyl-

ephrine. Denervation of the carotid and aortic pressoreceptors in the dog does not eliminate bradycardia induced by methoxamine as effectively as combined denervation of carotid, aortic, cardiac and pulmonary receptors.³¹ This suggests that intrathoracic pressoreceptors, particularly in the left ventricle, are activated by methoxamine. The activation is not direct (in a manner similar to that encountered by intracoronary injection of veratridine) but is probably indirect, initiated by the rise in left ventricular pressure.³¹ Corresponding information for phenylephrine is not available.

There is a clinical impression that bradycardia from methoxamine may occur even though mean arterial pressure does not rise significantly.³⁰ It is possible that the initial rise in pressure instantaneously activates pressoreceptors. The immediate response consists

of cardiac slowing which nullifies the rise in mean pressure, but the accompanying increase in pulsatile pressure may serve to perpetuate the continuous activation of pressoreceptors and cardiac slowing. This is not a remote possibility because the carotid sinus receptors have been shown by Neil and his collaborators³² to be sensitive to abrupt changes in pulsatile pressure. There is no direct evidence for this perpetuating mechanism with special reference to methoxamine. Simultaneous measurements of carotid sinus action potentials, pulsatile pressure and heart rate during a pressor response would offer supportive evidence.

The studies on ventricular arrhythmia indicate that methoxamine is unlike epinephrine in the following respects: it does not initiate contraction of the arrested ventricle in man;²⁹ in dogs, it does not initiate ventricular extrasystoles during anesthesia with chloroform,³³

cyclopropane³⁴ or methitalur;³⁵ it does not induce arrhythmias in dogs with ventricles arrested by vagal stimulation,³⁶ infarcted by ligation of one coronary branch³⁷ or subjected to myocardial injection of chemical irritants.³³ Gilbert and his collaborators³⁸ have characterized the lack of fibrillatory action of methoxamine as depression of electrical properties of the heart muscle consisting of prolongation of the ventricular action potential and of the absolute refractory period, slowing of auriculo-ventricular conduction and increased threshold to electrical stimulation. The studies on phenylephrine are less extensive. It may or may not initiate ventricular arrhythmia in human subjects^{12, 20} and in dogs.^{13, 15, 16}

(3) SINO-AURICULAR TACHYCARDIA AND DEPRESSION OF VENTRICULAR ARRHYTHMIA: Mephentermine is the only pressor agent which stimulates the sino-auricular node yet prevents

TABLE 3
COMPARATIVE EFFECTS ON CARDIAC OUTPUT IN MAN

Sympathomimetic Drugs and Doses	Number of Subjects (Method)*	%Δ Mean Arterial Blood Pressure†	%Δ Cardiac Output	%Δ Total Systemic Vascular Resistance	References
Epinephrine (i.v. up to 0.4 μg./kg./minute, s.c. or i.m. 0.5 to 0.7 mg.)	4 (F)	+/-	+	-	65
	13 (F)	+/-	+33	-	66
	11 (D)	+/-	+40	-30	70
	6 (B)	+/-	+52	-35	67
	6 (B)	+/-	+40	-	68
Levarterenol (i.v. up to 0.4 μg./kg./min.)	8 (F)	+	-	+	65
	13 (F)	+19	-6	+31	69
	6 (B)	+30	-32	+	68
Ephedrine (s.c. 50 mg.)	6 (B)	+10	+27	-13	67
Hydroxyamphetamine (i.m. 15 to 20 mg.)	5 (B)	+30	0	+	79
	2 (E)	+	0	+	80
Mephentermine (i.v. 5 to 20 mg.)	4 (F)	+	0	+	77
Metaraminol (i.v. 0.65 mg.)	7 (F)	+50	0	+55	76
Phenylephrine (i.v. 0.75 mg. or s.c. 3 to 10 mg.)	6 (B)	+35	-28	+	74
	14 (A)	+	-12	+	75

* B = ballistocardiography; D = dye dilution technique; E = ethyl iodide technique; F = Fick principle.

† A = acetylene rebreathing technique.

+/- = increase systolic but decrease diastolic; all other results consist of increases in both.

TABLE 4
COMPARATIVE EFFECTS ON CEREBRAL BLOOD FLOW (CBF), RESISTANCE (CVR)
AND METABOLISM (C-O₂) IN MAN

Sympathomimetic Drug (Dose)	Number of Subjects	CBF* (Control) %Δ	CVR† (Control) %Δ	C-O ₂ ‡ (Control) %Δ	References
Levarterenol (i.v. 6 to 28 μg./minute or i.m. 1 mg.)	3	(61) -8	(1.6) +37	(3.7) -5	148
	13	(61) -21	(1.3) -8	(4.0) -5	149
	4	(62) -12	(1.6) +53	(4.6) -15	150
Metaraminol (i.v. 50 mg./liter to increase pressure 40%)	7	(58) -19	(1.6) +50	(3.4) -6	150
Epinephrine (i.v. 20 to 70 μg./minute or i.m. 1 mg.)	7	(50) +22	(1.8) 0	(3.4) +23	148
	15	(66) +4	(1.2) 0	(4.2) -3	149
Mephentermine (i.v. total 30 mg. infusion)	9	(58) +4	(1.7) 0	(3.4) +24	153
Amphetamine (p.o. 20 mg. 5 to 11 days)	13	(67) +10	(1.28) -7	(4.1) +7	154
	2	(40) -2	(2.5) +4	(2.4) +4	152

* Cerebral blood flow by nitrous oxide method in ml./100 Gm./minute.

† Cerebral vascular resistance expressed in terms of ratio of mean blood pressure to CBF.

‡ Cerebral oxygen uptake is expressed in ml./100 Gm./minute.

or stops experimental arrhythmias. The specific antifibrillatory effects have been described by Oppenheimer and his collaborators⁴⁴⁻⁴⁶ as a shortening of refractory period and of conduction time in the dogs ventricular muscle. The antiarrhythmic effect in the human diseased heart has been proven.^{47, 48}

(4) SIGNIFICANCE OF ALTERATIONS IN RATE AND RHYTHM: The potential excitation of ventricular arrhythmias by epinephrine limits its use as a pressor agent. It is, however, the most widely used drug for resuscitating an arrested heart, although any of the other drugs (except methoxamine and phenylephrine) might be equally efficient. Epinephrine is the most potent of all pressor drugs, but the most powerful cardiac stimulant is isoproterenol, a systemic vasodilator and a depressor agent (table 1).

Methoxamine and phenylephrine do not stimulate sino-auricular rate directly but depress it by reflexly increasing vagal tone. The reflex bradycardia has been utilized to treat supraventricular tachycardia.⁴⁹⁻⁵² In some instances undesirable ventricular arrhythmias^{53, 54} and severe headache⁵⁵ have been elicited so use of these drugs requires caution.

(B) Force of Myocardial Contraction. The force of myocardial contraction can be measured in the isolated perfused heart and in the

heart *in situ* with a myocardiograph sutured to its ventricular surface. A compact strain gauge introduced by Walton and his collaborators⁵⁶ has made possible the study of force of contraction in unanesthetized dogs, and more recently in patients undergoing surgery with cardiopulmonary bypass.⁵⁷ In general, the effects of pressor drugs on ventricular force parallel those described for sino-auricular rate. All drugs that cause sino-auricular tachycardia (table 2) also stimulate the force of myocardial contraction, whereas methoxamine and phenylephrine do not stimulate the force of contraction.⁵⁸⁻⁶¹ The chronotropic and inotropic properties of the heart are, therefore, similarly affected by sympathomimetic drugs. There are exceptions to this rule. Phenylephrine which does not stimulate myocardial force in ordinary doses, stimulates it in large doses.^{27, 58, 62} Large doses of all other pressor agents, except epinephrine and levarterenol, depress myocardial force without direct inhibition of sino-auricular activity.^{59, 63, 64} The potential depressant action on the myocardium may be related to the reduction in cardiac output described below.

(C) Cardiac Output. The correlation of the effects of pressor drugs on heart rate and myocardial force in terms of cardiac output is not simple and straightforward. The avail-

able information is not consistent because of differences in techniques, species and pre-existing condition of the heart and blood vessels. Epinephrine and levarterenol have been investigated extensively but other pressor drugs have been inadequately studied. The grouping of drugs according to changes in cardiac output is arbitrary (table 3).

(1) **EPINEPHRINE:** Cardiac output is consistently increased following epinephrine regardless of species (man, dog, cat, rabbit). In normal human subjects, the maximum rise is about 50 per cent of control values.⁶⁵⁻⁶⁸ since systemic blood pressure is not increased proportionately, calculated systemic vascular resistance is reduced. The increase in cardiac output arises largely from the positive inotropic and chronotropic actions of the heart, but there may be vascular factors which will be considered below.

(2) **LEVARTERENOL:** Unlike epinephrine, the intravenous infusion of levarterenol usually reduces cardiac output in man. This was originally shown by Goldenberg and his collaborators⁶⁵ using the Fick principle, but others have offered confirmation using the same method^{66, 69} the indicator dilution technique⁷⁰ and ballistocardiography.^{67, 68} On the other hand, cardiac output in dogs is usually increased^{71, 72} so that there may be an important difference in cardiac action between man and dog. On the basis of output measurements, levarterenol stimulates the canine heart but not the human heart.

The discrepancy has been resolved by Wilber and Brust⁷³ who injected autonomic blocking drugs (tetraethylammonium bromide and atropine) in human subjects. Levarterenol infusion in such subjects increased cardiac output. When the blocking drugs were not used, the cardiac slowing accompanying the pressor response of levarterenol masked the cardiac stimulant action. The difference between levarterenol and epinephrine in man appears to be that reflex bradycardia by the former is more intense, whereas cardiac stimulation by the latter is more prominent. The results so far obtained from other amines are summarized in table 3. It is not possible to ascertain which ones are like epinephrine and which ones like levarterenol. Ephedrine causes increased cardiac output as measured by bal-

listocardiography⁶⁷ but confirmation by the Fick principle or by the dye dilution technique is not available. Phenylephrine reduces output.^{74, 75} No significant effect of metaraminol⁷⁶ and mephentermine⁷⁷ was observed. In dogs, direct measurements of pulmonary venous outflow show that:⁷⁸ hydroxyamphetamine and mephentermine behave like epinephrine in consistently increasing output; metaraminol, ephedrine, methylaminoheptane and methamphetamine have variable effects, and phenylephrine and methoxamine usually cause a reduction in output. These differences do not strictly conform to the known local cardiac actions but may reflect alteration in venous return initiated by peripheral vascular action of the drugs.

(3) **SIGNIFICANCE OF CHANGES IN OUTPUT:** Since the behavior of cardiac output is not certain for all drugs, it is impossible to utilize it as a reason to favor one drug. The available information for epinephrine and levarterenol is sufficient to discuss the factors that are likely to affect the ability of both drugs to cause an increase in output.

(a) Reflex bradycardia is largely responsible for reduction in output seen during the infusion of levarterenol in man. This has been discussed above (section II-C2).

(b) The amount of circulating blood may influence the ability of levarterenol to increase cardiac output of anesthetized dogs. Frank and his collaborators,⁸¹ using the Fick principle, noted an increase in output by levarterenol prior to bleeding but not during hemorrhagic shock. Other investigators have come to an opposite conclusion using the dye dilution technique.^{82, 83} The cardiometer and pulse contour method have been used^{83, 85} to note that epinephrine, ephedrine, phenylephrine, hydroxyamphetamine and methylaminoheptane increase the stroke volume in dogs even during hemorrhagic shock. Verification in hypotensive human subjects is necessary to determine if the output effects of these drugs are altered by bleeding.

(c) The reactivity of systemic veins has been regarded as an important factor in determining the cardiac response to sympathomimetic amines. Stead and Kunkel⁸⁶ have noted that in man the intramuscular injection of the pressor amine pholedrine (Paredrinol)

caused a rise in venous pressure accompanied by a reduction in blood flow to the extremities. They postulated that the rise in blood pressure is due chiefly to emptying of venous reservoirs by venous constriction leading to increased venous return. Perfusion of the systemic circulation in dogs has offered direct proof for the primary increase in venous return brought about by epinephrine^{87, 88} and levarterenol.⁸⁹

(d) The nature of the heart may be a determining factor in the ability of a drug to increase output. In experimental cardiac tamponade in the dog, an increase in blood pressure and output can be elicited by levarterenol,⁹⁰ epinephrine,⁹⁰ mephentermine,⁹¹ metaraminol⁹¹ and ephedrine.⁹⁰ All of these drugs are known myocardial stimulants so that the observed improvement in emptying, as well as filling of the ventricles, is partly due to myocardial action, although an increase in venous filling pressure would contribute. The intravenous injection of phenol in cats has been utilized by Tainter and Footer⁹² to induce cardiac depression which was reversed with injections of cardiac stimulants (epinephrine and hydroxyamphetamine). When the heart is infarcted, the desirability of cardiac stimulation will depend on the accompanying changes in cardiac metabolism.

D. Cardiac Metabolism and Coronary Blood Flow. The augmentation in cardiac output induced by pressor agents would be expected to increase cardiac work and oxygen uptake. Measurements in dogs receiving levarterenol and epinephrine indicate that both drugs increase myocardial oxygen uptake as well as coronary blood flow.⁹³⁻⁹⁶ The latter is partly dependent on the rise in systemic blood pressure, but in preparations in which blood pressure is constant, there is still a reduction in coronary vascular resistance. The explanation for the reduction in coronary resistance appears to be: (a) mechanical effect of systolic contraction; (b) vasodilation induced by the increase in cardiac metabolism, and (c) direct relaxation of coronary vascular wall. The acceptance of the latter in the dog's heart *in situ* is controversial. The arrested or fibrillating heart presumably free of myocardial influences that would alter flow shows vasoconstriction following levarterenol and epinephrine.⁹⁷ On

the other hand, measurements of phasic flows and pressures in the occluded artery show coronary dilatation by levarterenol.⁹⁸

The effects of other pressor agents on cardiac metabolism have not been investigated, although the behavior of coronary blood flow to some agents is known. West and his collaborators^{99, 100} have injected various amines directly into the dog's coronary artery and measured coronary venous outflow. Metaraminol, mephentermine and phenylephrine consistently caused an increase in coronary blood flow, similar to that induced by levarterenol and epinephrine. Since aortic blood pressure did not rise significantly, the increase in flow can be attributed to a local action on the heart. The force of contraction was increased simultaneously by each drug so that it was not possible to segregate ventricular and metabolic mechanisms from local vascular actions. Methoxamine caused neither a rise in coronary blood flow nor an increase in force of contraction. Its local effects on the coronary circulation appear unimportant so that an increase in flow can occur only by its pressor action.

An increase in coronary flow has been observed following intravenous injections in dogs of metaraminol,¹⁰¹ mephentermine,¹⁰² hydroxyamphetamine¹⁰³ and ephedrine.¹⁰⁴ There is no information regarding the effects of methylaminoheptane and methamphetamine but it would be surprising if they do not increase coronary blood flow because both pressor drugs stimulate the force of myocardial contraction.

Coronary blood flow has been studied in hypotensive dogs following the injection of levarterenol. The flow rises coincident with the increase in systemic blood pressure.^{81, 105} This observation illustrates the complex regulation of the coronary circulation. Since the improvement in coronary blood flow is unaccompanied by an increase in cardiac output (section II-C3), metabolic factors can be dismissed as a cause for the increase in flow. Instead, the rise in aortic blood pressure can be accepted as the most important cause.

Changes in coronary blood flow produced by vasopressors are of primary importance in the choice of a suitable pressor drug in patients in myocardial shock. It is desirable to improve coronary blood supply under these con-

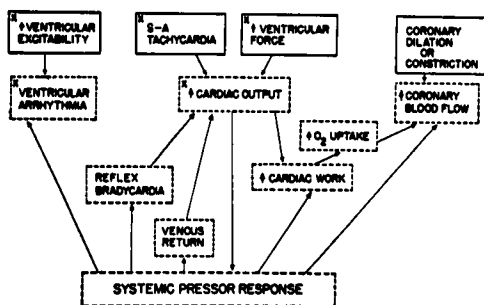


FIG. 1. Summary of cardiac effects of epinephrine. The solid boxes are primary effects and dotted boxes are secondary ones. Note that the systematic pressor response brought about by the increase in cardiac output may lead to reflex bradycardia, ventricular arrhythmia and increased coronary blood flow. The boxes marked with an (X) are not elicited by methoxamine.

ditions but it is not certain which of two approaches would be preferable: (a) improvement in flow produced exclusively by a rise in blood pressure induced by a drug that does not stimulate the heart (methoxamine), or (b) increase in flow by a drug which stimulates the heart with the risk of proportionately increasing the demand for oxygen by ventricular muscle (mephentermine). Some studies in dogs favor the latter because of an observed rise in oxygen tension in ischemic myocardium,¹⁰⁶ reduction in left atrial pressure of the embolized heart¹⁰⁷ and improvement in emptying of the left ventricle.¹⁰¹ Studies in patients have been difficult to interpret. It would be impossible to conduct a study of three groups of unselected cases of cardiogenic shock each group being given one of the two pressor agents or no drug. Another source of confusion is that the group (a or b above) into which levarterenol, the most widely used pressor amine, should be placed, is still uncertain. Reasons for some considering this drug a cardiac stimulant have been stated above (section II-C2), but unanimity is lacking. As long as this controversy continues, the effect of levarterenol may be incorrectly correlated so that the choice between (a) and (b) will remain unsettled.

(E) *Summary of Cardiac Effects.* The interrelationships of the various cardiac actions of the sympathomimetic pressor drugs are summarized in figure 1. There are four direct actions of epinephrine namely sino-auricular

tachycardia, increased ventricular force of contraction, and local coronary dilatation or constriction. No single mechanism is responsible for eliciting these actions. Although most pressor drugs increase ventricular force and excite the sino-auricular node and ventricular foci, methoxamine lacks the ability to do all of these, phenylephrine is suspected of being unable to induce sino-auricular tachycardia but elicits the two other actions and mephentermine is suspected of being devoid of proarrhythmic properties but induces the other actions. It is not possible to include local coronary vascular action in this comparison because it is controversial. Garb and his collaborators¹⁰⁸ have recently correlated cardiac metabolism with heart muscle function and concluded that the metabolic pathways for excitability and contraction are independent of each other.

The local effects of vasopressors on the heart can be measured clinically in a number of ways. Aside from the desired pressor action, there are electrocardiographic changes which reflect both local and reflex effects on the heart. Methoxamine, phenylephrine and levarterenol manifest chiefly reflex bradycardia whereas the other drugs produce both tachycardia and bradycardia. Cardiac output and coronary blood flow measurements are more complex of interpretation because they are dependent, not only on cardiac action but also on vascular action.

III. COMPARISON OF VASCULAR EFFECTS

The vascular effects of drugs in man have been investigated in many ways. One approach has been to utilize cardiac output measurements and use the calculated resistance values (pressure ÷ flow) to determine if the drug causes systemic vasoconstriction or vasodilatation. Levarterenol consistently causes a rise in resistance (vasoconstriction), whereas epinephrine consistently causes a fall (vasodilatation) (table 3). The other pressor agents have not been investigated extensively so it is not possible to decide which prototype they simulate. Methods of measuring blood flow in individual organs in man offers a convenient tool for determining vascular resistance but few drugs have been studied (see below). The major shortcoming of studying

organ blood flows is that it has not been possible to study local drug effects upon organs in man, with the exception of the extremities wherein drugs can be injected intra-arterially.

The data from animal experiments appear to be the only source of information regarding local vascular effects of drugs and this has been pursued by perfusion of excised vessels and organs, and by measurement of flow to organs *in situ*. Only the results of experiments performed during the last three years dealing with a systematic comparison of vascular effects of sympathomimetic drugs in anesthetized dogs will be discussed. The effects of vasopressors on the renal, pulmonary and carotid vascular beds have been reported elsewhere,^{81, 84, 78, 100-111} but the effect on mesenteric and limb vessels will be presented below.

The method used in previously reported experiments has been to insert a rotameter¹¹² into the artery of a particular organ. In the experiments reported presently, four arteries have been used, each supplied through a separate rotameter. The external iliac and superior mesenteric blood flows were measured in ten dogs (anesthetized with morphine-chloralose) and the common carotid and verte-

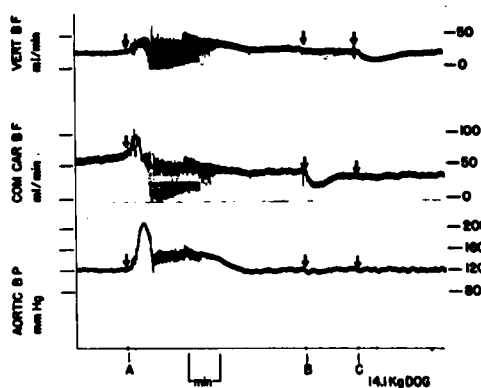


FIG. 2. Injections of levarterenol by the following routes: A = 3 μ g./kg. intravenously; B = 1 μ g. total into carotid artery distal to the flowmeter; C = 1 μ g. total into the vertebral artery also distal to its flowmeter. Note the immediate reduction in respective flows encountered following intraarterial injections which indicate vasoconstriction since aortic blood pressure remains unchanged. The intravenous injection causes an initial rise in flow coincident with the rise in pressure but the flows are then reduced in spite of persistence of hypertension. The aortic pressure was measured by a Statham transducer and its impulse was electrically integrated.

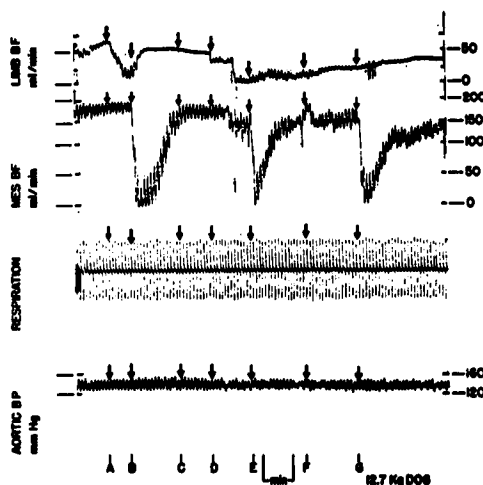


FIG. 3. Injections of levarterenol 5 μ g. total into: A = external iliac artery; B = mesenteric artery. Injections of methoxamine 100 microg. total into: C and D = external iliac but effects are delayed because of development of clot inside rotameter which was subsequently dislodged; E and G = superior mesenteric artery. F = superior mesenteric injection of methamphetamine 100 μ g. total dose which causes an increase in flow or vasodilatation. All other injections cause vasoconstriction.

bral arteries in another ten. Local vasoconstriction elicited by a drug was demonstrated by one or two ways. (a) When the intravenous injection caused an immediate increase in aortic pressure with a temporary rise in blood flow which either returned to control level or decreased below control level while the systemic blood pressure remained elevated (fig. 2 A). (b) When the intra-arterial injection caused an instantaneous decrease in blood flow without alteration in aortic pressure. There is a reduction of inflow to all organs when levarterenol, methoxamine and phenylephrine are injected individually indicating that these three drugs are local vasoconstrictors (fig. 2 B, C, fig. 3 A to D and fig. 4). On the other hand, vasodilatation could also be detected by intra-arterial injection. Following injection of mephentermine and methamphetamine there was a rise in blood flow with no change in aortic pressure and this combination was encountered in all organs (fig. 3E and F and fig. 4). The results of the experiments just described and those reported elsewhere are summarized in figure 5, wherein the pressor drugs are grouped into three classes: pre-

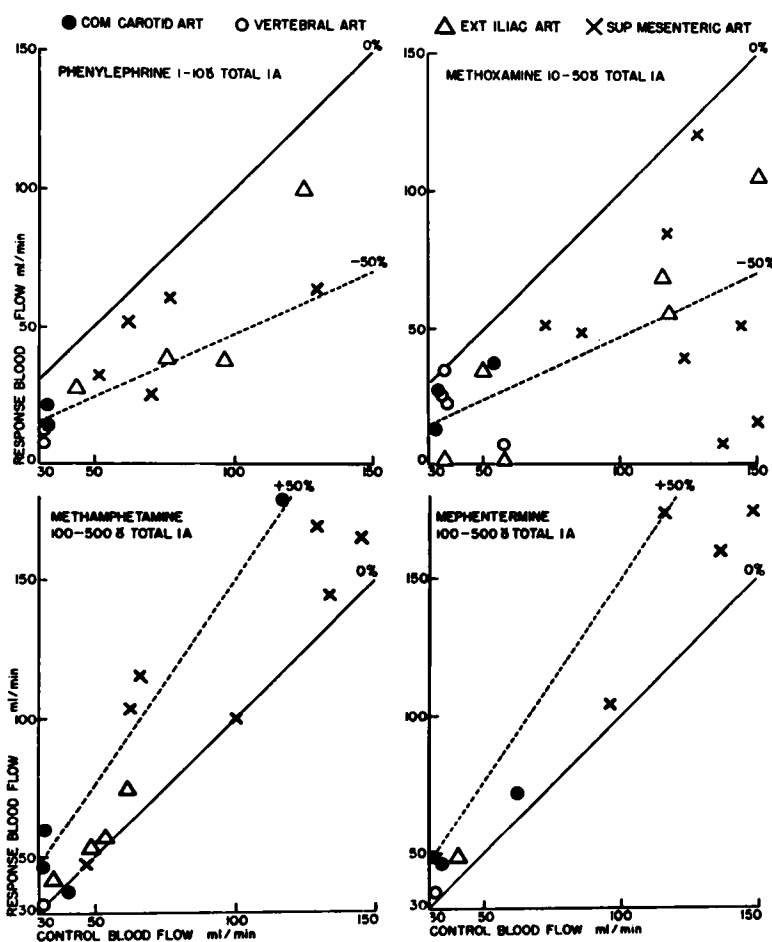


FIG. 4. Summary of local effects of phenylephrine (upper left), methoxamine (upper right), methamphetamine (lower left) and mephentermine (lower right) injected directly into the arterial supply. Control blood flows are on the abscissa and response on the ordinate. The diagonal lines represent areas of per cent increase and reduction.

dominantly vasoconstrictors, predominantly vasodilators and combined dilators and constrictors.

(A.) *Predominantly Vasoconstrictor.* Most pressor drugs are local vasoconstrictors. Levarterenol, phenylephrine and metaraminol constrict all vascular components of the systemic and pulmonary vessels. Ephedrine, methoxamine and hydroxyamphetamine constrict systemic vessels but have a variable or no effect on pulmonary vessels. An examination of the chemical structure of these six pressor agents has failed to reveal a chemical basis for the difference in extent of vasoconstriction.⁷⁸

(1) *EXTREMITIES:* Local vasoconstriction in the human extremities has been demonstrated only for levarterenol. Barcroft and Konzett¹¹³ injected this amine intraarterially and observed a reduction in blood flows to forearm and calf. Shaw, Papper and Rovenstine¹¹⁴ observed reduction in finger volume following the intravenous administration of phenylephrine and ephedrine. There is no corresponding information for other vasoconstrictors in man; but animal experiments have shown the local constriction induced by phenylephrine,¹¹⁵ ephedrine¹¹⁶ and hydroxyamphetamine.¹¹⁷ It would be desirable in both human subjects and animals to compare the sensitivity of cutane-

ous and muscle vessels, as well as the sensitivity of arteries and veins. This has been pursued largely for epinephrine and levarterenol and will be discussed below (section III-C).

The practical importance of local vasoconstriction in the extremities lies in the fact that the limbs may be a potential reservoir from which blood may be shifted into more vital organs during the pressor response. The amount of blood translocated from the extremities of the dog during infusion of levarterenol has been studied by Shadle, Zukol and Diana.¹¹⁸ Veins are suspected to be the major source of the blood. The ability of venous strips to contract has been shown at least for metaraminol,¹¹⁹ but the other vasoconstrictors have not been tested.

(2) **SPLANCHNIC ORGANS:** Bearn, Billing and Sherlock¹²⁰ demonstrated in man a reduction in hepatic blood flow following the infusion of levarterenol. Grayson and Swan¹²¹ using thermocouples applied to colonic mucosa showed a reduction in temperature indicating vasoconstriction induced by the same amine. The situation in the splanchnic bed is similar in many respects to that of the extremities. There is no information regarding the effects of other vasoconstrictors in man. In animals vasoconstriction by levarterenol,¹²²⁻¹²⁵ hydroxyamphetamine¹²⁶ and ephedrine¹⁰ has been reported. The studies are in addition to those mentioned above. As a potential reservoir, the splanchnic bed is more complex than that of the extremities because the amount of blood in mesenteric and splenic vessels is influenced not only by the vascular smooth muscle but also by the splenic capsule and the intestinal wall.

(3) **KIDNEYS:** An increase in renal vascular resistance in man using clearance methods has been demonstrated for levarterenol,¹²⁷⁻¹³³ methoxamine,¹³⁴ phenylephrine,¹³⁵ metaraminol⁶⁸⁻¹³⁶ and ephedrine.¹³⁷⁻¹³⁹ Although renal blood flow is reduced by the first four, there is usually no reduction in flow by ephedrine indicating that the local vasoconstriction is masked by a rise in pressure. This may be an item in favor of ephedrine but the role of drug induced renal vasoconstriction in determining renal function requires elucidation. In hypotensive subjects following the injection

of hexamethonium salt or suffering from hemorrhagic shock, Moyer and his collaborators¹⁴⁰⁻¹⁴² have shown that levarterenol infusion may actually augment renal blood flow with improvement in urine formation. Techniques more direct than clearance methods have been used in dogs. The results show a reduction in renal blood flow and urine formation in normal¹⁴³⁻¹⁴⁷ as well as in hypotensive dogs.⁸¹ This discrepancy may be due either to difference in species or in techniques of measuring blood flow. Until it is resolved, it is safe to remember that a reduction in renal blood flow and urine formation has not yet been excluded when any vasoconstrictor drug is used to improve hypotension.

(4) **BRAIN:** Levarterenol and metaraminol manifest similar actions on cerebral blood flow in man as determined by the nitrous oxide method.⁴⁸⁻¹⁵⁰ Both drugs cause reduction in cerebral blood flow in spite of a pressor response, indicating that the cerebral vessels are constricted (table 4). There is no information concerning the effects of the five other vasoconstrictors in man. The results of vertebral arterial studies in dogs (summarized in fig. 5) cannot be transferred freely to man because important vascular differences exist between both species.¹⁵¹ Cerebral excitation would be expected from ephedrine so that the increase in cerebral oxygen uptake might initiate an increase in blood flow in a manner similar to amphetamine.¹⁵²

(5) **LUNGS:** The pulmonary vascular effects of sympathomimetic drugs in experimental animals have been received elsewhere.^{78, 155} Cardiac catheterizations in human subjects have shown a pulmonary vasoconstrictor action for levarterenol⁶⁵ and metaraminol.⁷⁶ The conclusion is based on the observation that the rise in pulmonary arterial pressure is usually accompanied by a fall in cardiac output. The pulmonary hypertensive action of ephedrine¹⁵⁶ cannot be interpreted as due to pulmonary vasoconstriction because output was not measured concurrently. Since the vascular effects of ephedrine in the dog's lungs are variable (fig. 5) the pulmonary hypertensive action of this alkaloid may be entirely due to increased pulmonary blood flow.

Pulmonary edema developing during the infusion of levarterenol and phenylephrine for

	EXTERNAL ILIAC	COMMON CAROTID	VERTEBRAL ARTERY	SUPERIOR MESENTERIC	RENAL	PULMONARY
LEVARTERENOL	CONSTRICT					
METARAMINOL	CONSTRICT					
EPHEDRINE	CONSTRICT					VARIABLE
HYDROXYAMPHETAMINE	CONSTRICT					VARIABLE
METHOXAMINE	CONSTRICT					VARIABLE
PHENYLEPHRINE	CONSTRICT					
METHAMPHETAMINE	DILATE				VARIABLE	DILATE
MEPHENTERMINE	DILATE				VARIABLE	DILATE
METHYLAMINOHEPTANE	DILATE				VARIABLE	
EPINEPHRINE	CONSTRICT AND DILATE				CONSTRICT	

FIG. 5. Summary of vascular effects derived from anesthetized dogs. This is based on experiments represented in figures 2 to 4, and on experiments reported previously.^{31, 44, 78, 109-111} "Variable" means either no local change or variable effect on arterial flow following intraarterial injections.

myocardial shock has been reported.¹⁵⁷ This may serve to limit the use of drugs that elevate pulmonary arterial pressure when the heart has been damaged. The exact cause of the edema induced by pressor agents may be the outcome of: (a) rise in hydrostatic pressure in the pulmonary capillaries and/or (b) unequal failure of both ventricles which are unequally stimulated by drugs. The end result is that the right ventricle pumps more blood than the left indicating pulmonary congestion and edema.

Systemic shock of pulmonary embolism has been treated by levarterenol infusion.¹⁵⁸⁻¹⁶⁰ There are actually two considerations in the drug therapy of pulmonary embolism and levarterenol satisfies only one of these; namely, that the systemic shock may be reversed. The existing pulmonary hypertension may be exaggerated by levarterenol which may in turn initiate failure of the right ventricle (cor pulmonale). Sympathomimetic drugs that do not constrict pulmonary vessels of dogs may be more desirable (methoxamine, ephedrine, hydroxyamphetamine and the next group of dilators) but unfortunately their pulmonary vascular effects have not been confirmed in man.

(6) SIGNIFICANCE OF VASOCONSTRICTOR ACTION: Local vasoconstriction induced by levarterenol (and the 5 other drugs) appears to be the most important cause for its systemic

pressor action. Such vasoconstriction is selective in that the coronary and cerebral vessels are either spared or are weakly responsive. The more intense vasoconstriction induced by these drugs in the renal, limb and splanchnic vessels agrees with the general concept of the distribution of sympathetic vasoconstrictors, i.e., the blood flow to the vital organs (heart, brain and lungs) are spared when the sympathetic nervous system is activated. Levarterenol is unique among these vasoconstrictors because it is regarded as the chemical mediator for impulses reaching the sympathetic neuro-effector function (see references cited by von Euler).⁹

Although all six pressor drugs can initiate vasoconstriction, there are important differences in the dose required, the duration of action and the dependability. Levarterenol is the most potent but also the shortest acting so that it is administered exclusively by intravenous infusion. It is poorly absorbed orally and other parenteral routes are not recommended chiefly because of intense local vasoconstriction which might terminate in necrosis and sloughing. Several cases of cutaneous necrosis at the site of venous infusion,¹⁶¹⁻¹⁶⁷ as well as remote from the site¹⁶⁸ have been reported. Intra-arterial injection of tolazoline¹⁶² and subcutaneous infiltration of piper-

oxan¹⁶³ and phentolamine¹⁶⁴⁻¹⁶⁷ have been recommended as pharmacological antagonists. (table 5).

The other vasoconstrictors are weaker than levarterenol and have more prolonged duration of action. The intravenous route is effective but the intramuscular route may be preferred (table 5).

(B.) *Predominantly Vasodilators.* The most surprising item of information summarized in figure 5 is the ability of methamphetamine,

TABLE 5
COMPARATIVE EFFICIENCY OF SYMPATHOMIMETIC PRESSOR AGENTS
DURING SPINAL ANESTHESIA

Sympathomimetic Drugs	Intramuscular Dose,* mg.	Number of Cases	% Cases with Inadequate Maintenance†	Average % Fall in Blood Pressure	References‡
No medication	—	500	65	36	218
	—	100	90	23	220
	—	200	65	27	221
Ephedrine	50	500	30	14	218
	25	100	59	10	220
	50	100	30	4	220
	50	200	10	12	221
	50	151	21		222
	48	150	36		30
	25-50	250	18		219
	25-50	200	10		224
	20-40	177	20		226
Methamphetamine	20-30	500	20	3	218
	15	100	40	7	220
	25	152	28		222
	2 (?)	150	29		30
	10-30	250	6		219
	(?)	1202	13		227
Methoxamine	10-15	500	26	10	217
	10-15	500	21		30
	5-10	200	11		225
	(?)	703	19		227
Hydroxyamphetamine	10	500	38	19	218
Mephentermine	30	200	17	12	221
	30-45	367	22		223
	20-40	1471	15		226
	(?)	115	24		227
	30	800	5		228
Methylaminoheptane	50	150	35		30
	50	250	7		219
	50	150	35		227
Phenylephrine	5-6	146	47		222
Metaraminol	3-5	240	10		225

* (?) indicates dose unusually low or dose unspecified.
† Criteria for inadequacy were as follows:
Fall in blood pressure greater than 25% of control.^{20, 217, 218, 221, 228}
Fall in blood pressure greater than 20 mm.^{220, 226}
No additional dose needed to maintain blood pressure.^{219, 220, 223, 225, 227}
‡ Reference number indicates those results that have been derived by the same group of investigators.

mephentermine and methylaminoheptane to dilate blood vessels in dogs. The blood flow experiments reported above have been preceded by other data. Frumin, Ngai and Papper¹⁶⁹ noted that injections of methamphetamine into the dog's femoral artery caused an immediate vasodilation which may or may not be followed by vasoconstriction. Ahlquist¹⁷⁰ reported similar femoral vasodilatation induced by methylaminoheptane and Sarnoff and his collaborators¹⁷¹ observed a generalized vasodilatation by mephentermine. In man, the studies are confined to methamphetamine. Allen¹⁷² noted increased forearm flow whereas Churchill-Davidson and his collaborators¹⁷³ described increased renal blood flow following intramuscular administration of methamphetamine. Both responses differed from those elicited by ephedrine and levarterenol in the two organs, respectively. Methamphetamine^{156, 174} and mephentermine⁷⁷ have been shown to cause a rise in pulmonary arterial pressure but this rise may be entirely a manifestation of increased cardiac output elicited by both drugs.

Nasal mucosal vessels appear to be exempt from the generalized vasodilatation induced by these drugs. Measurement of nasal pressure in the dog (with posterior and anterior nares closed) show that these three agents injected intravenously cause a reduction in pressure which has been interpreted to mean shrinkage of the nasal mucosa by local vasoconstriction.¹⁷⁵⁻¹⁷⁸ This may not be the only interpretation because intracarotid injections of the same drugs augment carotid blood flow.¹¹¹ It is possible that other extracranial vessels are so dilated that the reduction in flow in the nasal mucosa is entirely a passive phenomenon. It is also possible that when these drugs are applied topically to the nasal mucosa that a reflex vasoconstriction can be elicited which may account for the nasal decongestion.

The above evidence that methamphetamine, mephentermine and methylaminoheptane, local vasodilators is little compared to the more extensive evidence collected for those pressor drugs that are vasoconstrictors (section III-A). One particular type of desirable confirmatory evidence would be to measure blood flow (of any organ) in the same human subject using a vasoconstrictor and a vasodilator. If the

vasodilator is proven to be devoid of local constrictor action, its mechanism of causing systemic arterial hypertension becomes an important consideration. There are two alternatives for accounting for a rise in aortic blood pressure by drugs that are local vasodilators: (a) Powerful stimulation of the heart with the increase in cardiac output overcoming the peripheral vascular action (section II-C). (b) Excitation of the medullary and supramedullary centers inducing sympathetic vasoconstriction overcoming the local action. The second alternative is not remote because all three drugs are known to be central nervous system stimulants. On the other hand, Bromage¹⁷⁹ showed that methamphetamine becomes a more powerful pressor agent in subjects with a high sensory level of spinal anesthesia indicating that the sympathetic nervous system is not essential in effecting the pressor response.

C. Combined Vasoconstrictor and vasodilator. Epinephrine is the only example of a pressor drug that induces both vasoconstriction and vasodilatation. This was originally demonstrated in ergotized animals in which a previous pressor response to epinephrine was converted into a depressor response. The conversion is due to blockade by ergot alkaloids of the vasoconstriction but sparing the vasodilation induced by epinephrine. In the absence of blockade, both types of vascular actions are elicited. Recent experiments have shown that in man as well as in animals, the constrictor action is more marked in the skin vessels but the reverse is true for muscle vessels.¹⁸⁰⁻¹⁸³ Haddy and his collaborators¹⁸⁴ have suggested that epinephrine constricts small vessels in the dog's limbs (less than 0.5 mm. in diameter), but not the larger vessels which are constricted by levarterenol. Eckstein and Hamilton¹⁸⁵ have come to a similar conclusion from experiments in the human forearm in which the large veins responded by a greater fall in distensibility (contraction) to levarterenol, as compared to epinephrine.

The renal vessels are similar to the skin vessels in that they respond to epinephrine predominantly by vasoconstriction.¹⁴⁸ The weakest concentration does not induce vasodilatation but other sympathomimetic vasodilators (including isoproterenol, line 3 of table 1) can cause vasodilatation.¹¹⁰ The ab-

sence of a sympathomimetic vasodilator mechanism previously implied by Spencer¹⁴⁷ appears to be an open question particularly because a number of sympathomimetic vasodilators can dilate renal vessels.¹¹⁰

The cerebral and coronary vessels predominantly dilate after epinephrine (sections II-D and III-A and Table 4), but pulmonary vessels appear to constrict.⁷⁸ The activity of the splanchnic bed remains uncertain because of its numerous vascular components. Constriction of the portal vein, intrahepatic vessels and hepatic artery^{124, 186, 187} and dilation of hepatic and splenic veins are suspected to occur.^{188, 189}

The vasodilator actions of epinephrine appear to be more important than the vasoconstrictor. Epinephrine in man causes a rise in systolic pressure with a fall in diastolic pressure, yet the rise in cardiac output is proportionately larger than the rise in mean pressure. The calculated systemic vascular resistance drops chiefly as a result of vasodilatation (table 3). This may be a limitation to the use of epinephrine as a pressor agent but is not as serious a limitation as the ventricular arrhythmias that accompany the pressor response (section II-A). Although the inhibitory action on blood vessels may be undesirable when epinephrine is used as a pressor agent, there are situations in which such action is desired. Improvement in blood flow to the extremities by vasodilatation, bronchodilatation and relaxation of gastrointestinal sphincters can be induced by epinephrine and by a number of derivatives that are more selective in their actions (table 1). The ethoxy derivative of methoxamine (Compound 45-50) is a selective pulmonary vasodilator and is currently undergoing clinical trial of its abilities to relieve pulmonary hypertension.⁷⁸

D. Factors Limiting Effectiveness of Pressor Agents. Eckenhoff and Dripps¹⁹⁰ have discussed possible reasons for lack of success in eliciting a pressor response with levarterenol, reasons which apply to other pressor drugs as well. The list includes inadequate dose, failure of drug to reach the site of activity, mechanical interference to blood flow, failure of the heart, inadequate blood volume and failure of vascular smooth muscle to contract. The last two items deserve additional discussion because there is serious need for correla-

tion of available facts as well as confirmation directly from patients that are resistant to pressor agents.

(1) **CIRCULATING BLOOD VOLUME:** Hemorrhagic shock in dogs is characterized by intense peripheral vasoconstriction. In spite of this, a satisfactory pressor response during shock has been encountered with levarterenol,^{81, 191} metaraminol,¹⁹² hydroxyamphetamine,¹⁹³ phenylephrine¹⁹⁴ and methoxamine.¹⁹⁵ All these drugs cause vasoconstriction, but it is possible to explain the improvement in blood pressure exclusively by vasoconstriction for the last two drugs. The other three may improve cardiac output although as stated above this component usually disappears in hemorrhagic shock (section II-C). The compensatory vasoconstriction of hemorrhage appears to be a submaximal one upon which sympathomimetic constriction can still be added.

(2) **HORMONAL AND ELECTROLYTE BALANCE:** There is sufficient information to justify the belief that hormonal imbalance can interfere with the cardiovascular effects of sympathomimetic amines. Most data show that corticosteroids, corticotropic hormones and thyroid hormones potentiate the cardiac stimulant, as well as the vasoconstrictor action of epinephrine and levarterenol, in animals,¹⁹⁶⁻¹⁹⁸ but contradictory results have also been reported.¹⁹⁹⁻²⁰⁰ The positive findings bear some relationship to the depletion of potassium from the heart and vessels that respond to levarterenol.²⁰¹⁻²⁰⁴ It is possible that the lack of such hormones interferes with the cationic shift in organs so that sympathomimetic amines become inactive.

(3) **ACIDOSIS:** Burget and Vissher reported the dependence of epinephrine effect on blood pH in cats.²⁰⁵ Recent experiments have shown that inhalation of carbon dioxide interferes with the pressor response,^{206, 207} and cardiac stimulant response²⁰⁸ to epinephrine, levarterenol and metaraminol in dogs. The ultimate site of interference is suggested by Mohme-Lundholm²⁰⁹ who postulates that vascular effects of levarterenol are dependent on the production of lactic acid by the vascular smooth muscle. Barcroft and Cobbald showed similar increase in lactic acid content of venous blood draining the forearm.²¹⁰

(4) **GANGLIONIC BLOCKADE:** Duner and von

Euler²¹¹ observed that following the infusion of levarterenol in cats, there is a secondary fall in blood pressure explained by ganglionic blockade. This fall has been previously encountered by Churchill-Davidson²¹² in patients. It is possible that ganglion blockade may occur during infusion, but it is not detectable because levarterenol may act distal to the ganglia. The fact that bradycardia usually occurs during the pressor response to levarterenol means that the usual doses do not block parasympathetic ganglia.

IV. DEPENDABILITY OF PRESSOR AMINES DURING SPINAL ANESTHESIA

The final consideration in the selection of a pressor drug might be to determine which one is most effective and dependable. A review of the clinical reports dealing exclusively with one agent would lead to an erroneous conclusion. Comparative efficiency rather than individual effectiveness is the primary concern and this can be derived only from controlled studies.

Unlike sedatives and analgesics, the action of pressor agents can be detected objectively, but it is surprising to note that the available literature allows a reasonable comparison only in the situation in which spinal anesthesia is the cause of the hypotension. There are numerous reasons for this. Patients to whom spinal anesthesia is given are usually encountered under circumstances in which blood pressure is routinely measured, whereas nonsurgical patients develop hypotension unexpectedly. The practice of giving pressor agents in spinal anesthesia dates back to 1927²¹³ where as their use in myocardial shock began only in 1949 (references cited²¹⁴⁻²¹⁶). The hypotension of spinal anesthesia can be explained principally by the temporary paralysis of the sympathetic vasomotor outflow, but the underlying causes of orthostatic hypotension, traumatic shock and myocardial shock are fundamentally more complex and ill defined. The hypotension of spinal anesthesia is usually benign, but the hypotension of myocardial infarction is malignant and forces the use of all available measures. It therefore discourages a comparative study of pressor drugs.

The incidence of hypotension during spinal anesthesia has been reported as ranging from 65 to 90 per cent of patients, and the average reduction in pressure, about one fourth to one third of the control level.⁵⁷⁻⁵⁹ All pressor drugs, with the exception of epinephrine and levarterenol, have been used to prevent hypotension (table 5). There is no study by the same group of investigators of all eight drugs. The largest number of drugs studied by any one group is five. Dripps, Deming and King^{217, 218} noted that the lowest incidence of hypotension (fall in mean pressure greater than 20 per cent of control) was encountered in a group of 500 patients given methamphetamine prior to the spinal and in another group given ephedrine combined with pituitrin. The incidence of hypotension was 25 per cent and was compared to other drugs as follows: methoxamine 26 per cent, ephedrine alone 30 per cent, hydroxyamphetamine 38 per cent and no medication 65 per cent.

The apparent greater effectiveness of one drug on the basis of a lower incidence of hypotension is not a compelling factor in its favor for three reasons. (a) The order of preference would depend upon which particular report is considered. Ephedrine and methamphetamine have been investigated by four other groups (table 5). The lower incidence of hypotension for methamphetamine reported by Dripps and Deming²¹⁸ has been confirmed by two studies^{30, 219} but a higher incidence has also been reported.^{220, 222} (b) The inadequacy of a single prophylactic dose is usually overcome by an additional dose of the same drug so that inadequacy may be simply a reflection of the biological variation in sensitivity to a drug encountered in a group of patients. (c) There is no assurance when dealing with a particular patient that the response to a specific drug will be adequate, in spite of the fact that the reported incidence of its inadequacy is the lowest.

The ability of all pressor drugs to support blood pressure during hypotension has been established. The reported differences in inadequacy can be ignored temporarily as a major consideration in choosing drugs, until a controlled study involving all of them is completed.

V. SUMMARY OF CARDIOVASCULAR ACTIONS

A comparison of the combined cardiac and vascular effects of the ten pressor agents appears in figures 6 to 10. Only three items of information are certain: (a) all pressor drugs are clinically effective; (b) some drugs directly stimulate sino-auricular rate and ventricular contraction whereas others lack one or both actions, and (c) some drugs elicit local vasoconstriction, others local vasodilation and one elicits both. The effects on cardiac output, ventricular rhythm, myocardial metabolism, and individual organ blood flows are uncertain so that the final grouping into five classes is entirely based on items (a), (b) and (c).

(A) *Epinephrine* (fig. 6). The major features of epinephrine are its cardiac stimulation and its ability to constrict and dilate blood vessels. The end result in man is increased cardiac output and increased blood flow to all organs except the kidneys. It is the most potent drug known to stimulate an arrested heart, but the accompanying possibility of initiation of ventricular arrhythmias, limits its use as a pressor agent.

EPINEPHRINE		
CARDIAC STIMULATION	INCREASED CARDIAC OUTPUT	VASOCONSTRICTION & VASODILATION
<ul style="list-style-type: none"> ↑ SA RATE ↑ SA RATE (REFLEX) ↑ VENTR ARRHYTHMIA ↑ VENTR FORCE ↑ CARDIAC METABOLISM 	<ul style="list-style-type: none"> ↑ CORONARY BF ↑ CEREBRAL BF ↑ LIMB BF ↑ MESENTERIC BF ↑ RENAL BF PULMONARY HYPERTENSION 	<ul style="list-style-type: none"> ↑ AORTIC PRESSURE ↑ AORTIC PRESSURE VS CONSTRICTION CHIEFLY BY ↑ BF
SYSTEMIC HYPERTENSION CHIEFLY BY INCREASED OUTPUT		

FIG. 6. Hemodynamic pattern of epinephrine.

LEVARTERENOL AND METARAMINOL		
CARDIAC STIMULATION	DECREASED CARDIAC OUTPUT	VASOCONSTRICTION
<ul style="list-style-type: none"> ↑ SA RATE ↑ SA RATE (REFLEX) ↑ VENTR ARRHYTHMIA ↑ VENTR FORCE ↑ CARDIAC METABOLISM 	<ul style="list-style-type: none"> ↑ CORONARY BF ↑ CEREBRAL BF ↑ LIMB BF ↑ MESENTERIC BF ↑ RENAL BF PULMONARY HYPERTENSION 	<ul style="list-style-type: none"> ↑ AORTIC PRESSURE LOCAL CONSTRICTION OVERCOMES EFFECT OF INCREASED PRESSURE COMBINED ↑ BF AND CONSTRICTION
STIMULATION MASKED BY REFLEX		SYSTEMIC HYPERTENSION CHIEFLY BY CONSTRICTION

FIG. 7. Hemodynamic pattern of levarterenol and metaraminol. The (?) for arrhythmias pertains to conflicting results summarized in table 2.

EPHEDRINE AND HYDROXYAMPHETAMINE		
CARDIAC STIMULATION	INCREASED CARDIAC OUTPUT (?)	VASOCONSTRICTION
<ul style="list-style-type: none"> ↑ SA RATE ↑ SA RATE (REFLEX) ↑ VENTR ARRHYTHMIA ↑ VENTR FORCE ↑ VENTR FORCE (LARGE DOSE) ↑ CARDIAC METABOLISM(?) 	<ul style="list-style-type: none"> ↑ CORONARY BF ? CEREBRAL BF ? LIMB BF ? MESENTERIC BF ↑ RENAL BF PULMONARY HYPERTENSION 	<ul style="list-style-type: none"> ↑ AORTIC PRESSURE ↑ AORTIC PRESSURE VS CONSTRICTION CHIEFLY BY ↑ BF
SYSTEMIC HYPERTENSION CHIEFLY BY INCREASED OUTPUT(?)		

FIG. 8. Hemodynamic pattern of ephedrine and hydroxyamphetamine. The (?) for output pertains to conflicting results summarized in table 3. The (?) preceding organ blood flows mean that this information is still not known in human subjects.

(B) *Levarterenol and Metaraminol* (fig. 7). Although both drugs are capable of stimulating ventricular force, the end result in man appears to be either no change or a reduction in cardiac output. The best explanation for the absence of increased output appears to be the reflex bradycardia initiated by the pressor response. The pressor response is entirely due to vasoconstriction unless reflex pathways are blocked (by atropine or ganglion blocking drugs) in which case the increased output may contribute to the rise in blood pressure. Blood flow to brain, kidneys, splanchnic organs and extremities is usually reduced, at least for levarterenol. The desirability of cardiac stimulation when both agents are used in myocardial infarction remains to be proven. The potency of levarterenol, as well as its short duration of action, limits its administration exclusively to intravenous infusion. The corresponding features of mataraminol, however, allow its use by intramuscular injection. The renal vasoconstriction by both drugs may complicate its use by the appearance of anuria, but this is true for all the other vasoconstrictors (next two groups), so that this cannot be utilized as an exclusive undesirable feature of levarterenol and metaraminol.

(C) *Ephedrine and Hydroxyamphetamine* (fig. 8). These two pressor agents are essentially similar in action to levarterenol and metaraminol in that they potentially can bring about cardiac stimulation and vasoconstriction. The difference is that in man the cardiac stimulant action of ephedrine and hydroxy-

METHOXAMINE AND PHENYLEPHRINE		
NO CARDIAC STIMULATION	DECREASED CARDIAC OUTPUT	VASOCONSTRICTION
↓ SA RATE (REFLEX) ↓ VENTR ARRHYTHMIA → VENTR FORCE ↑ VENTR FORCE (LARGE DOSE) ? CARDIAC METABOLISM	↓ CORONARY BF ? CEREBRAL BF ? LIMB BF ? MESENTERIC ↓ RENAL BF PULMONARY HYPOTENSION	↓ AORTIC PRESSURE ↓ AORTIC PRESSURE VS CONSTRICTION CONSTRICTION PRE-DOMINANT CHIEFLY BY ↓ BF
SYSTEMIC HYPERTENSION SOLELY BY CONSTRICTION		

FIG. 9. Hemodynamic pattern of methoxamine and phenylephrine. The (?) preceding cardiac metabolism and organ flows mean that confirmation in man are necessary. The increase in ventricular force may be encountered for phenylephrine but not for methoxamine.

METHAMPHETAMINE, MEPHENTERMINE, AND METHYLAMINOHEPTANE		
CARDIAC STIMULATION	INCREASED CARDIAC OUTPUT (?)	VASODILATATION
↑ SA RATE (REFLEX) ↓ VENTR ARRHYTHMIA ↑ VENTR FORCE ? CARDIAC METABOLISM	↑ CORONARY BF (?) ↑ CEREBRAL BF (?) ↑ LIMB BF (?) ↑ MESENTERIC BF (?) ↑ RENAL BF (?) PULMONARY HYPERTENSION	PREDICTED FROM DILATOR ACTION CHIEFLY BY ↑ BF
SYSTEMIC HYPERTENSION SOLELY BY INCREASED OUTPUT (?)		

FIG. 10. Hemodynamic pattern of methamphetamine, mephentermine and methylaminoheptane. The (?) preceding cardiac metabolism indicates that this has not been measured. The (?) following organ flows indicate necessity for measurements in human subjects although the indicated increases can be predicted from animal experiments.

amphetamine is more conspicuous than the vasoconstrictor action so that cardiac output and organ blood flow are more likely to be increased. The hemodynamic picture is more closely similar to that of epinephrine but both agents lack the ability to dilate blood vessels. The depressor action following large doses of both drugs encountered in animals is due to the onset of tachyphylaxis to their primary actions and the appearance of myocardial depression seen with larger doses.

(D) *Methoxamine and Phenylephrine* (fig. 9). The principal cause for the pressor action of methoxamine and phenylephrine is vasoconstriction. The former is devoid of any stimulant action on the heart, but the latter is

suspected of having some which is less than that of known cardiac stimulants (classes A, B, C and E). Cardiac output should be expected to be reduced and organ blood flow also reduced but confirmatory measurements in man are lacking. From a theoretical standpoint, this class of pure vasoconstrictors would be the complete pharmacological antagonist for the hypotension associated with spinal anesthesia in which vasodilatation but no cardiac depression occurs. In myocardial shock the desirability of sparing the infarcted heart from any form of stimulation needs clarification.

(E) *Methamphetamine, Mephentermine and Methylaminoheptane* (fig. 10). These last three agents cause hypertension chiefly by cardiac stimulation in spite of initiating vasodilation. In terms of the above classes of drugs, it is the pattern of epinephrine (class A) minus that of methoxamine (class D). The studies of blood flows in man are disappointingly limited but on the basis of animal studies, no reduction in flow to any organ would be expected to occur. Renal complications are unlikely because renal blood flow is not likely to be reduced. The important hemodynamic abnormality in myocardial shock is reduced cardiac output and systemic vasoconstriction. From this standpoint, this class of pressor agents (cardiac stimulant and vasodilator) would be the logical pharmacological antagonist rather than any one of the other four.

It is important to emphasize the fact that the available information on the mechanism of cardiovascular effects of pressor agents has been derived from two types of preparations: anesthetized animals and unanesthetized human subjects. The connecting link of studies on anesthetized subjects would be a welcome addition that might help resolve some of the existing discrepancies.

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