TRAUMATIC SHOCK.

IX. PRESSOR THERAPY: THE EFFECT OF PAREDRINE (p-HYDROXY-a-METHYLPHENYLETHYLAMINE HYDROBROMIDE) ON THE CIRCULATION IN HEMORRHAGIC SHOCK IN DOGS[1,2]

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INTRODUCTION

Vasoconstriction is a normal response to a fall in blood volume, but excessive vasoconstriction caused by pressor drugs, while it raises the arterial pressure, is considered to be undesirable because it decreases the already diminished flow through capillaries (1, 2). Pressor drugs are therefore said to be harmful in shock in which there is a diminished blood volume, although many physicians still regard them as beneficial. The aim of the present investigation was to inquire into the benefit or harmfulness of vasoconstriction consequent to pressor therapy by studying the effect of a pressor drug upon the circulation of unanesthetized animals in hemorrhagic shock. Paredrine (p-hydroxy-a-methylphenylethylamine hydrobromide) was chosen because of its ability to raise arterial and venous blood pressure solely through vasoconstriction and because of its lack of effect on metabolic activity (3, 4).

METHOD

Forty-one mongrel dogs, weighing 7 to 15 kgm., were used. Morphine sulfate, in doses of 2.0 mgm. per kgm., was given intramuscularly one-half to 2 hours before the start of each experiment; exposure of arteries and veins and tracheotomy were performed under local anesthesia. General anesthesia was induced in a few dogs, in 1 by ether for nephrectomy, and in 2 by intraperitoneally administered nembutal for laparotomy and portal vein puncture. All other nephrectomies and kidney mobilizations were done under local anesthesia. Superior sagittal sinus blood was obtained by direct puncture after trephining the skull. The trephining was done under ether anesthesia, from which the animal was allowed to recover completely before the start of the experiment.

After control measurements were made, the dogs were bled fractionally from the femoral artery until the arterial blood pressure fell to 70 mm. Hg or below and showed no tendency to recover spontaneously. The total amount of blood removed varied from 19.0 to 47.0 ml. per kgm. of body weight, and the period of bleeding ranged from 10 to 30 minutes. Paredrine, in doses ranging from 2.0 to 20.0 mgm., was given intravenously or both intravenously and intramuscularly at intervals in shock, before and after transfusion. Blood oxygen analyses were done at the time of the maximal blood pressure response.

Arterial blood pressures were measured with a mercury manometer by needle puncture of the femoral artery. Venous blood pressures were registered with a water manometer after needle puncture of the femoral vein. Mixed venous blood was obtained from the right auricle by means of a straight glass tube passed through the left external jugular vein. Other venous blood specimens were taken by direct venipuncture. Samples of blood for determination of oxygen and carbon dioxide content were taken under oil; the gas analyses were carried out by the manometric method (5).

RESULTS

Effect of paredrine on arterial and venous blood pressures after hemorrhage. A rise in arterial pressure occurred following 20 of 22 initial injections of paredrine, given at various intervals during shock resulting from hemorrhage (Figure 1). The rise varied from 15 to 60 mm. Hg and averaged 35 mm. Hg; its duration averaged 30 minutes. When the drug was given both intramuscularly and intravenously, the effect lasted somewhat longer, averaging 45 minutes. In several experiments, such combined administration was followed by elevation of the arterial blood pressure to approximately 100 mm. Hg for 60 to 90 minutes. Subsequent injection usually produced diminishing responses, and if

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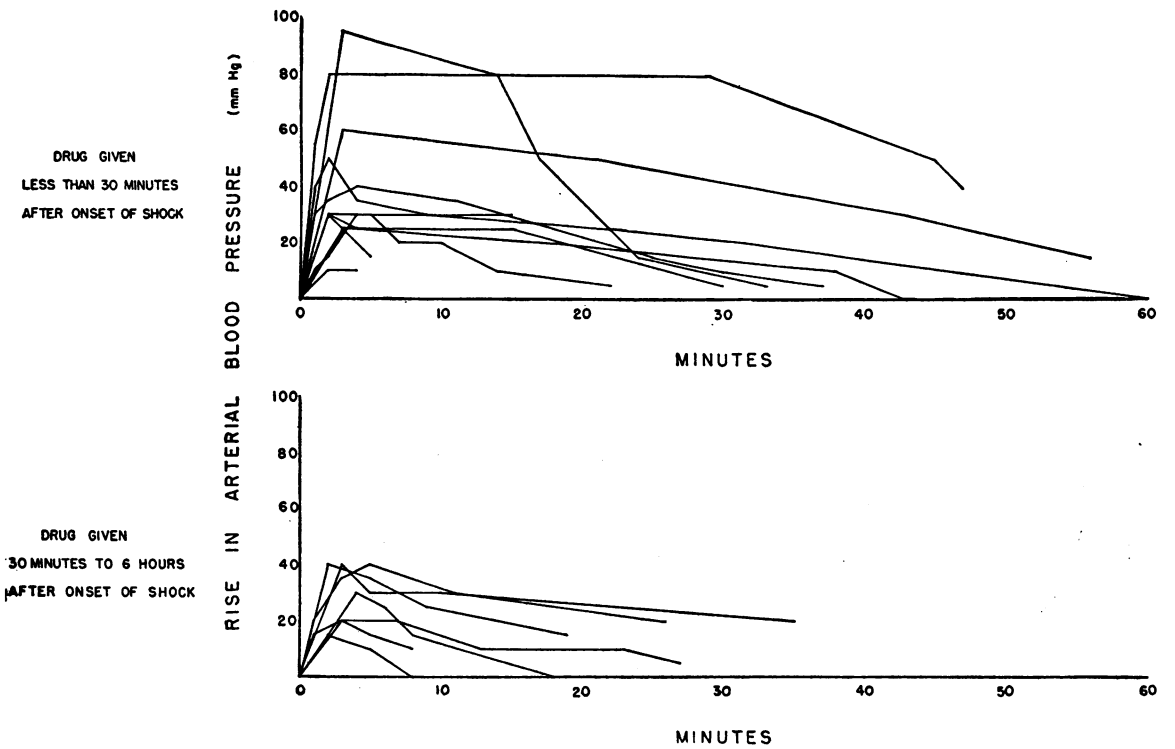

FIG. 1. THE BLOOD PRESSURE RESPONSE TO AN INITIAL DOSE OF PAREDRINE

the first dose was large (20 mgm.), a second injection was usually completely ineffective. Most of the doses were large enough to elicit the maximal effect of the drug, so that there was little correlation between the size of the dose and the degree or duration of effect.

Rises in venous pressure occurred at the same time as the rise in arterial pressure. The rise in venous pressure ranged between 3.0 and 6.0 cm. of water, averaging 2.3 cm.

The pulse rate usually fell markedly as the blood pressure rose, decreasing 50 to 100 beats a minute.

The development of unresponsiveness to paredrine. The rise in arterial and venous pressures after the administration of a first dose of paredrine was greater and more persistent early in shock than later, but the decreasing effectiveness of an initial injection did not parallel the increasing duration of shock.[3] Animals remained responsive to a first dose after as much as 6 hours of shock (Figure 1). However, repeated injection of paredrine, even early in shock, quickly reduced the responsiveness of the dogs, so that when the full effect of 20 mgm. had worn off, most of the dogs became completely unresponsive to the drug (Figure 2). Transfusion did not restore responsiveness, even in the dogs which survived, in the period of several hours during which they were observed. Responsiveness to a *first* dose of paredrine could be demonstrated, however, late in "irreversible" shock after unsuccessful transfusion.

Effect of paredrine on blood flow after hemorrhage. The arterio-venous blood oxygen difference was uniformly increased in the animals in shock, varying directly with the severity of shock. The injection of paredrine caused no increase in the oxygenation of the mixed venous blood, even though arterial and venous pressures rose (Table IA).

Samples of blood from the external jugular, portal, and femoral veins gave no evidence of preferential improvement in the flow through any of these beds (Table IA). During the maximal blood pressure response, an increase in alertness and activity was observed in most dogs.

[3] In the charts and figures, as well as in the text, the duration of shock is arbitrarily measured from the time the arterial blood pressure fell below 70 mm. Hg.

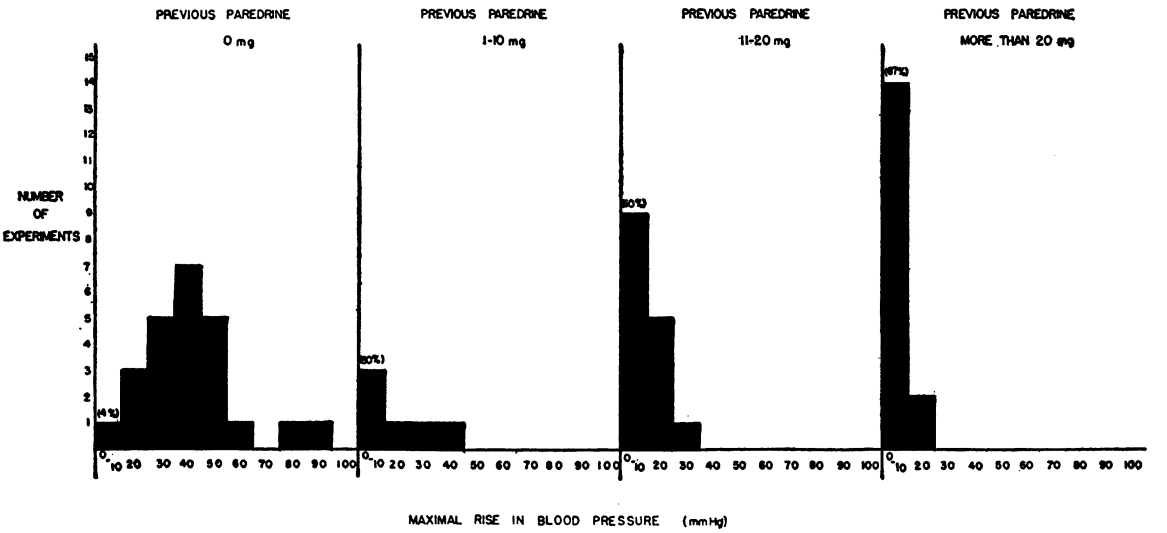

FIG. 2. THE EFFECT OF PREVIOUS PAREDRINE ADMINISTRATION UPON THE ARTERIAL BLOOD PRESSURE RESPONSE

In an effort to determine whether this reflected an increase in cerebral blood flow, the oxygen content of the blood of the superior sagittal sinus was analyzed before and during the period of paredrine action. Such reduction in arterio-venous oxygen difference as was found by this technic (Table IB) was small, occurred only early in shock, and was of very brief duration (Dogs No. 304 and No. 306).

TABLE IA

The effect of paredrine upon the arterial blood pressure and the arterio-venous blood oxygen difference in hemorrhagic shock

Source of venous blood	Dog No.	Before paredrine		After paredrine	
		Art. B.P.	O_2 A-V	Art. B.P.	O_2 A-V
		mm. Hg	*volumes per cent*	*mm. Hg*	*volumes per cent*
Right auricle	9–3	50	12.7	100	9.2
	8–31	60	7.7	120	8.9
	8–28	60	11.0	120	10.9
	8–26	60	6.6	90	9.9
	8–24–2	50	7.9	85	9.8
	8–24–1	55	11.0	100	13.2
	8–20–2	30	16.0	10	15.1
	8–20–1	35	10.3	85	10.6
	8–18–2	45	10.9	65	15.4
	8–18–1	40	11.7	30	13.0
	304	65	9.2	110	9.2
	305	40	11.8	115	13.3
	303	70	9.3	120	10.2
	302	45	10.2	110	8.9
	301	40	15.0	65	16.1
	302	35	13.7	65	14.1
	303	50	11.8	55	13.1
Femoral vein	8–26	60	11.8	90	9.6
	8–31	60	18.1	120	12.1
	9–3	50	17.4	100	17.3
Jugular vein	8–31	60	11.2	120	10.6
	9–3	50	13.0	100	14.1
Portal vein	8–31	60	7.5	120	6.8
	9–3	50	10.1	100	12.0

TABLE IB

The effect of paredrine upon the arterial blood pressure and the arterio-venous blood oxygen difference in hemorrhagic shock

Source of venous blood	Dog No.	Duration of shock	Before paredrine		After paredrine	
			Art. B.P.	O_2 A-V	Art. B.P.	O_2 A-V
		minutes	*mm. Hg*	*volumes per cent*	*mm. Hg*	*volumes per cent*
Superior sagittal sinus	304	15	65	9.0	110	8.4
		10 min. later			100	9.7
	305	20	40	13.9	115	11.1
	303	25	70	7.1	120	6.4
	302	35	45	8.1	110	5.6
	306	30	65	8.0	100	6.2
		3 min. later			90	7.5
	301	90	40	14.4	65	13.9
	305	95	35	11.3	65	11.0
	306	150	25	9.2	25	9.0
	303	170	50	9.2	55	11.7

Effect of transfusion after paredrine in hemorrhagic shock. After a period of hemorrhagic shock during which paredrine had been given until it no longer produced a pressor response, transfusion was followed by a rise in blood pressure which was greater than the average rise of similarly bled and transfused dogs which had not received paredrine, reaching an average level

TABLE II

The effect of transfusion immediately after an ineffective injection of paredrine in hemorrhagic shock

Dog No.	Volume bled	Duration of shock	B.P. before transfusion	Transfusion		B.P. after transfusion		Survival	Remarks
				Volume bled	Kind of blood	Highest level	Compared to original level		
	ml. per kgm.	*hr. min.*	*mm. Hg*	*per cent*		*mm. Hg*	*mm. Hg*		
7	45	1 26	70	80	own fresh	185	+80	+	
8	35	2 2	65	83	own fresh	200	+95	+	
17	34	1 33	50	85	own fresh	175	+85	+	
20	28	1 22	55	76	own fresh	145	+45	sac.	Laparotomy. Portal vein puncture. Nembutal anesthesia.
24	28	1 31	25	89	own fresh	155	+55	sac.	Laparotomy. Portal vein puncture. Nembutal anesthesia.
18	33	1 33	30	85	own fresh	110	=	0	
19	34	1 24	55	84	own fresh	110	+15	+	
1	34	3 20	30	100	foreign stored	110	=	+	
2	25	6 20	30	100	foreign stored	82	−20	0	
3	34	3 35	20	100	foreign stored	140	+50	+	
4	41	1 40	10	100	foreign stored	130	=	0	
5	32	1 35	18	75	foreign stored	90	−10	0	
6	37	1 17	40	100	foreign stored	110	+20	0	
10	31	4 8	45	100	foreign incub.	105	−15	+	Blood incubated at 37° C. for 18 hours.
11	50	4 31	35	63	foreign incub.	125	+10		Blood incubated at 37° C. for 12 hours.
				84	own fresh	135	+20	+	Second transfusion after max. response to first.
12	35	3 25	50	60	foreign fresh	110	−10	+	
13	39	4 35	60	67	foreign fresh	125	+ 5	+	
16	47	23	35	75	foreign fresh	130	+30	+	
15	37	34	30	83	foreign fresh	110	=	0	
14	46	2 36	25	83	foreign fresh	120	+15		
				93	own fresh	130	+25	+	Second transfusion after max. response to first.
21	38	51	60	100	foreign fresh	125	+20		
				70	own fresh	155	+50	+	Second transfusion after max. response to first.
22	39	1 15	65	100	foreign fresh	140	+25		
				66	own fresh	135	+20	+	Second transfusion after max. response to first.
25	21	1 34	55	100	own fresh	85	−20	sac.	Bilateral nephrectomy. Ether anesthesia.
26	32	1	50	87	own fresh	130	+35	sac.	Bilateral nephrectomy. Local anesthesia.
27	19	47	60	100	own fresh	135	+20	sac.	Bilateral nephrectomy. Local anesthesia.
28	19	5 15	55	100	own fresh	90	=	sac.	Bilateral kidney mobilization. Local anesthesia.
29	32	3 34	55	84	own fresh	120	+10	sac.	Bilateral kidney mobilization. Local anesthesia.

28 mm. Hg higher than the control level. The transfusions were given within 5 to 10 minutes after a completely ineffective injection of paredrine. Eight dogs received their own blood. In 4 instances, blood pressure levels of 180 to 200 mm. Hg were reached within 10 minutes after completion of the transfusion; the hypertension subsided gradually over 20 to 30 minutes and these 4 dogs went on to recovery. No post-transfusion blood pressure above 140 mm. Hg was observed in 7 similar experiments in which the infused blood was freshly taken from another dog, or in 6 experiments in which the source of the transfusion was refrigerated blood gathered in the previous week (Table II). Two other dogs transfused with their own fresh blood had blood pressure responses within the average range, but the remaining 2, in spite of nembutal anesthesia and laparotomy for portal vein puncture, had post-transfusion blood pressure levels which were well above average. In 4 experiments, following a transfusion of fresh blood from another dog, a second transfusion with the dog's own fresh blood did not produce an unusual rise in blood pressure.

The relationship of the post-transfusion blood pressure level to a possible synergism of paredrine with the renal pressor mechanism was studied in

5 dogs as follows: prior to the production of hemorrhagic shock, 3 dogs had bilateral nephrectomy and 2 underwent exposure and mobilization of both kidneys. No hypertensive response occurred in these 5 experiments following the development of tachyphylaxis to paredrine and transfusion of the dogs' own fresh blood.

DISCUSSION

Contraction of the volume of the vascular bed must always occur when the blood volume decreases. Loss of blood, however, is usually followed by additional arteriolar constriction sufficient in many instances to raise the arterial pressure to or toward normal. The usefulness to the animal in shock of this spontaneous vasoconstriction has not been established. One investigator (6) found that, at a given blood pressure level in shock, sympathectomized dogs had a greater volume flow through the paw than non-sympathectomized animals. His conclusion that the elimination of sympathetic vasoconstriction delayed the onset of "shock" can be questioned because the sympathectomized animals were bled less to reach the shock blood pressure level and accordingly had larger blood volumes. Thus, in totally sympathectomized animals, the arterial blood pressure falls in proportion to reduction in blood volume, reaches low levels after withdrawal of only 10 to 20 per cent of blood volume, and shows no tendency to recover after cessation of bleeding (6, 7). This is in contrast to unsympathectomized animals in which blood pressure is maintained or tends to return toward normal until 30 to 50 per cent of the blood volume is removed. This author's data (6) do not indicate whether the sympathectomized dog is more resistant to the development of shock by bleeding than an unsympathectomized dog suffering the loss of the same volume of blood. Other workers (7) found that the removal of 12 to 15 per cent of the blood volume of sympathectomized cats resulted in irreversible shock, whereas the normal animal tolerated the withdrawal of 40 percent. The experiments they report are too few to establish conclusively that normal vasoconstriction protects against the lethal effect of hemorrhage. Two others (8) found a wide variation in the maintenance of peripheral vascoconstriction in the later phases of hemorrhagic shock. If the normal vasoconstrictor response is useful, reenforcement of this response by pressor therapy might also be useful.

On the other hand, excessive vasoconstriction has been shown to be harmful. It has been suggested (9) that the sympatho-adrenal activity provoked by fear, pain, cold, and excitement intensifies shock. Others have pointed out the vascular collapse which follows the hypersecretion of epinephrine of pheochromocytoma (10) and have shown that shock can be produced by epinephrine injection (11). One worker (12) believed that a reduction in plasma volume occurred as a result of epinephrine injection, but this finding was disputed by others (13). The amounts of epinephrine required to produce shock are far in excess of the physiologic range as measured (14), and the continuous injection in dogs, over a period of days to weeks, of the amount of epinephrine (3.0 μg. per kgm. per minute) shown (14) to be secreted in response to strong afferent stimulation, does not cause shock (15). Moreover, epinephrine is a stimulant of metabolic activity as well as a vasoconstrictor (16) and it distorts carbohydrate metabolism (17), and therefore may be harmful, particularly in shock, by actions unrelated to vasoconstriction. This distinction is supported by the lack of evidence of harm resulting from maximal doses of paredrine.

The experiments of this study do not indicate whether the added vasoconstriction induced by paredrine is beneficial or harmful in hemorrhagic shock. The duration of action of paredrine was limited by the development of refractoriness to the drug which was not determined by the severity of the shock state, so that the development of "tachyphylaxis" was not an index of its severity or of the degree of "reversibility." No comparison is attempted between untreated animals and those given paredrine as far as tolerance to blood loss is concerned, because unselected and unanesthetized dogs vary so greatly in their response to hemorrhage and to the subsequent reinfusion of blood that no consistent control pattern is available against which to measure the effects of a therapeutic agent.[4]

[4] Since the completion of this manuscript, a study with this intent has been published (David F. Opdyke, The

During the period of paredrine-induced elevation of blood pressure, there was no change in the oxygenation of the venous blood returning to the heart. This suggests that the increased arterial pressure was so balanced by the narrowing of the blood vessels as to result in an unchanged total blood flow.

The assumption is frequently made by clinicians that a return toward normal arterial pressure produced by vasoconstriction in states of diminished blood volume results in an altered distribution of the total blood flow, with improved flow through critical circuits such as the cerebral, coronary, or renal. This implies a lesser degree of vasoconstriction of those beds which are to benefit. With reference to the cerebral circulation, the experimental evidence offered on this point has been conflicting. Using thermocouple implantation, one author (18) concluded that the cerebral cortical vessels of the anesthetized cat do not constrict in response to epinephrine. Others (19) demonstrated a striking increase in the velocity of cerebral blood flow when the blood pressure was elevated in cats. Two workers (20), however, using a bubble flow-meter in the carotid artery of anesthetized monkeys, found that epinephrine injected into the carotid artery caused a striking fall in intracranial blood flow without change in systemic blood pressure. On the other hand, epinephrine given intravenously caused an increase in brain blood flow early, as the systemic blood pressure rose; as the systemic blood pressure declined, the carotid flow fell proportionally in half the cases, but fell to a definitely subnormal flow in the remainder.

In the present study, no increase in the oxygen content of the sagittal sinus blood was noted during the period of elevated blood pressure. This may be an inadequate measure of cerebral circulation and perhaps fails entirely to reflect changes in blood flow through the brain stem. Indeed, dogs have been observed to resume spontaneous respiration following paredrine injection and rise in blood pressure in a phase of hemorrhagic hypotension so extreme that normal breathing had stopped. Nevertheless, the data failed to support the concept that vasoconstrictor drug therapy produces a useful or protective redistribution of blood flow in hemorrhagic shock. However, the effect of paredrine on flow through many important circulatory beds, *i.e.*, the hepatic, coronary, and renal, was not studied.

The lengthening of diastole consequent to slowing of the heart rate after the injection of paredrine may have improved cardiac function.

A significant feature of the circulatory failure of shock is the inadequacy of the volume of venous return flow. Paredrine raises the venous pressure, apparently by direct constrictor action on the veins (3). During the period of increased venous pressure produced by paredrine in animals in shock, there was no increase in cardiac output. This remained the case when paredrine was given after the blood volume had been restored by transfusion.

The finding after transfusion of a level of blood pressure higher than the control (pre-hemorrhage) level in most of the animals treated with paredrine suggested that the paredrine injection in shock before transfusion became active after transfusion in spite of the lack of response to paredrine just before transfusion and to the injection of paredrine in transfused dogs. A possible explanation for this phenomenon is that hypertensin and paredrine are synergistic in their effect upon the blood pressure. Renin increases in the blood of the dog in hemorrhagic shock as hypertensin-precursor disappears (21, 22) and the transfusion, by restoring the precursor, might permit the rapid formation of abnormally large amounts of hypertensin which might then enter into such a synergism with the circulating paredrine. A protective function of the renal pressor mechanism in hemorrhagic shock has been claimed (23). The experiments designed to test whether a hypertensin-paredrine synergism operated to produce either (*1*) the moderate post-transfusion elevation in blood

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survival of dogs treated with neosynephrine during the production of hemorrhagic shock. Am. J. Physiol, 1944, **142**, 576). Neosynephrine was given by continuous intravenous infusion to dogs anesthetized with morphine and sodium barbital during the course of hemorrhagic shock. The survival after transfusion of these animals was found to cover a wide range, the average of which exceeded that of an untreated control group. However, no greater incidence of recovery resulted from this treatment. The neosynephrine given did not keep the arterial pressure of the treated dogs above 70 to 75 mm. Hg.

pressure observed in most dogs which had received paredrine during the period of shock, or (*2*) the marked elevations in blood pressure observed among the animals which received their own blood, were not conclusive. All 5 dogs which had undergone kidney surgery prior to the induction of shock received their own blood in transfusion and none made a hypertensive response. This cannot be attributed to an absence of renin, unless it can be shown that simple mobilization of the kidneys completely inhibits renin formation. On the other hand, bilateral nephrectomy under local anesthesia did not prevent 2 dogs from reaching post-transfusion blood pressure levels 20 to 35 mm. Hg above their control levels. More direct evidence that a paredrine-hypertensin synergism was not operating after transfusion in these experiments was supplied by the finding that the synergistic action of paredrine and hypertensin is abolished when tachyphylaxis to paredrine has developed (24). The fact that the marked hypertensive response occurred only in the animals which had been reinfused with their own blood is not explained; the distribution may have been chance.

CONCLUSIONS

1. Vasoconstriction is not maximal in hemorrhagic shock in the dog; arterial and venous pressures can be raised for considerable periods of time by paredrine.

2. The responsiveness to paredrine diminishes or is lost late in shock or after repeated dosage.

3. The increase in arterial and venous pressures is not accompanied by an improvement in blood flow. The increase in alertness and activity following effective paredrine injection in shock is not explained.

4. These experiments do not indicate whether the vasoconstrictor effect of paredrine during hemorrhagic shock exerts a useful or harmful effect.

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