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Influence of Anesthetic Agent on Response to Hemorrhagic Hypotension

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Survival times and hemodynamic, metabolic, and sympathoadrenal responses to progressive hemorrhagic hypotension were determined in dogs subjected to blood removal of 10 ml/kg/30 min during MAC anesthesia with cyclopropane, isoflurane, and halothane. Mean survival times ranged from 146 minutes (cyclopropane plus succinylcholine) to 247 minutes (halothane). Initially, hemodynamic function was better maintained with cyclopropane, with or without succinylcholine, and arterial epinephrine and lactate concentrations increased earlier than with isoflurane or halothane. However, with further unreplaced blood loss, hemodynamic function, O_2 uptake, and acid–base balance were sustained better with either isoflurane or halothane than with cyclopropane. Further studies showed that increased lactate concentration resulted from increased epinephrine concentration. During hemorrhage the initial maintenance of arterial pressure by agents such as cyclopropane, which enhances sympathoadrenal response to hemorrhagic hypotension, is achieved by mechanisms lessening the ability to survive additional blood loss. These augmented responses are, overall, undesirable additives to the anesthetic circumstance. (Key words: Hemorrhage: inhalation anesthetics; Shock: inhalation anesthetics; Anesthetics, gases: cyclopropane, shock; Anesthetics, volatile: halothane, shock; Anesthetics, volatile: isoflurane, shock; Metabolism: hemorrhage.)

ALTHOUGH it is generally agreed that anesthetic agents differ in the ways they modify sympathoadrenal activity, it is not clear how important these differences are and whether there are practical clinical implications. The lack of definition of importance of these matters is undoubtedly related to the technical difficulties of making pertinent observations in man and to the reservations regarding studies in other species. We have been encouraged to continue studying this in the dog for two reasons. First, the responses of the laboratory model are compatible with our ideas as to how modification of sympathoadrenal activity alters the response to unreplaced blood loss.[1-2] Second, we see in the dog in this circumstance the same better initial hemodynamic support that has largely provided the rationale for the use of cyclopropane in this situation in man.[3-4]

The current studies examine survival time and associated hemodynamic and metabolic events with progressive unreplaced blood loss during four different anesthetic circumstances. With infusion studies we also examined the effect of increased concentrations of epinephrine or norepinephrine or both on lactate concentrations and *vice versa*. The findings are consistent with and support the views of others regarding the undesirable aspects of increased sympathoadrenal reactivity induced by anesthesia.[5-6]

Material and Methods

The animals used for these studies (at 37 C) were unpremedicated, fasted mongrel dogs (weights, 20 ± 2 kg). In all, endotracheal anesthesia was maintained at the concentrations of cyclopropane (17.5 per cent), isoflurane (1.48 per cent), or halothane (0.87 per cent) that have been established to equate with MAC.[7-8] All dogs were ventilated with the anesthetic agent in O_2 and N_2, $\dot{V}$ and F_{IO_2} being appropriately adjusted to provide a Pa_{CO_2} of 40 ± 2 mm Hg and a Pa_{O_2} of 150 ± 10 mm Hg initially and throughout the control period. No medication other than those specifically mentioned was given.

Catheters were placed in the pulmonary and

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carotid arteries for measurement of pressures (strain gauge), determination of cardiac output (indocyanine green dilution technique), and sampling of mixed venous and arterial blood for determination of 1) O_2 content (calculated from P_{O_2} and oxyhemoglobin concentration), 2) arterial P_{O_2}, P_{CO_2}, and pH (electrodes, 37 C), and 3) arterial concentrations of lactate (L) (enzymatic methods), and plasma concentrations of epinephrine (E) and norepinephrine (N) (according to the method previously described[9]). In the blood-removal studies only, plasma volume was determined during the control period from activity in plasma samples obtained 10 and 20 minutes after intravenous injection of RISA of known total activity, and these results were used in conjunction with the hematocrit of a central blood sample to estimate whole-blood volume. In all studies, observations were confined to the second half of a 30-minute period and were made in duplicate except for catecholamines (single) and cardiac output and $(a\text{-}\bar{v})_{O_2}$ (in triplicate).

Four types of studies were done.

1) The effects of the anesthetic agent on survival time and the hemodynamic, metabolic, and catecholamine responses to progressive unreplaced blood loss were determined in four groups of five dogs each in one of the following four circumstances: cyclopropane plus succinylcholine, 150 mg/hour (C_3H_6/SCh); C_3H_6 alone; isoflurane alone; or halothane alone. After control observations had been made in each group, blood was removed at 10 ml/kg at 30-minute intervals and observations were continued until death (EEG interpretation) occurred. In these studies, blood removed for sampling was treated as a component of the total blood removed.

2) Another study was concerned with the responses to infusion of lactic acid in amounts necessary to span the ranges of blood lactate increases observed in the unreplaced-blood-loss study. Five dogs were observed during anesthesia with C_3H_6/SCh prior to and during two 30-minute periods in which appropriate amounts of lactic acid in 5 per cent glucose in distilled water were given by continuous intravenous infusion.

3) Another study involved the responses during anesthesia with either C_3H_6/SCh (three dogs) or isoflurane (three dogs) to continuous intravenous infusion of E, N, or E plus N in amounts sufficient to span the ranges observed in the unreplaced-blood-loss study. After control observations had been made, one type of infusion was studied in each dog and five sets of observations were made at progressively greater infusion rates of E (0.050 to 0.80 μg/kg/min), N (0.0125 to 0.200 μg/kg/min), or a combination of E and N at these rates.

4) In the fourth study, the effect of passage of time on the response to unreplaced blood loss was assessed in one dog each during anesthesia with C_3H_6/SCh and with halothane. In these studies, following control determinations, blood (35 ml/kg) was removed and observations were repeated at 30-minute intervals for at least 5 hours. The blood removed initially was used to replace, volume for volume, all blood loss related to sampling.

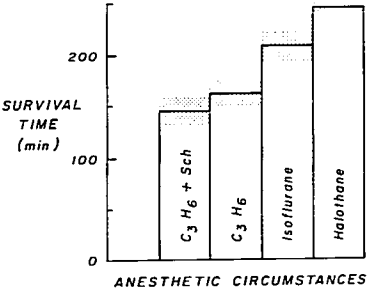

FIG. 1. Survival times with progressive hemorrhage (10 ml/kg/30 min) in different anesthetic circumstances (means ± SE).

Results

Mean survival time with progressive blood removal of 10 ml/kg each 30 minutes was least (146 min) during anesthesia with C_3H_6/SCh and greatest (247 min) with halothane (fig. 1). These significantly different survival times were not ascribable to differences in initial blood volumes which, overall, had a mean value (±SD) of 105 ± 12 ml/kg and were not significantly different between groups.

Control observations and responses during the first four increments of blood removal are summarized in table 1. Tabulation was not carried beyond this point due to progres-

TABLE 1. Effects of Hemorrhage (10 ml/kg/30 min) on Cardiac Output; O_2 Uptake; Mean Arterial Pressure; Arterial Epinephrine, Norepinephrine, and Lactate; Arterial *p*H and Buffer Base; and Mixed Venous P_{O_2} in Different Anesthetic Circumstances (Five Dogs Each; Means ±SE)

Anesthetic Circumstance	Blood Removed, ml/kg	Cardiac Output, l/min/m²		Oxygen Uptake, ml/min/kg		Mean Arterial Pressure, mm Hg		Arterial Concentration of Epinephrine, μg/l		Arterial Concentration of Norepinephrine, μg/l		Arterial Concentration of Lactate, μmol/ml		Arterial *p*H		Buffer Base		Mixed Venous P_{O_2}	
CaHa/SCh	0	3.60	0.20	6.81	0.44	150	5	1.14	0.18	0.15	0.09	3.08	0.23	7.30	0.01	41	1	63	1
	10	2.28	0.23	5.94	0.32	128	4	1.21	0.20	0.21	0.09	2.61	0.18	7.31	0.03	41	1	55	1
	20	1.41	0.19	5.01	0.44	102	6	2.06	0.36	0.43*	0.09	2.33	0.19	7.31	0.03	41	1	48	1
	30	0.90	0.21	4.20	0.40	65	10	3.34*	0.76	0.82*	0.17	2.85	0.29	7.28	0.03	40	1	39	2
	40†	0.58	0.22	3.25	0.75	49	8	5.50*	1.29	1.70*	0.44	5.86*	1.37	7.18	0.06	33	4	31	4
CaHa	0	3.70	0.15	7.45	0.08	133	6	0.76	0.09	0.16	0.08	2.39	0.66	7.34	0.02	43	0	60	1
	10	2.62	0.18	6.62	0.28	123	6	0.77	0.09	0.23	0.07	2.36	0.63	7.32	0.01	42	1	54	1
	20	1.80	0.21	5.80	0.36	116	6	1.06	0.11	0.29*	0.05	2.57	0.43	7.30	0.01	41	1	49	1
	30	1.13	0.18	4.91	0.38	89	10	1.48*	0.24	0.49*	0.06	2.88	0.37	7.28	0.01	40	1	41	2
	40	0.65	0.15	3.59	0.54	52	16	1.89*	0.16	0.59*	0.07	6.00*	1.05	7.18	0.05	34	3	31	3
Isoflurane	0	2.89	0.39	5.24	0.33	81	8	0.34	0.11	0.16	0.08	1.84	0.16	7.38	0.02	44	1	53	3
	10	2.28	0.29	5.10	0.18	70	7	0.53	0.12	0.21	0.07	1.79	0.25	7.36	0.02	44	1	48	3
	20	1.83	0.18	4.81	0.20	70	6	0.69	0.30	0.28*	0.06	1.92	0.26	7.33	0.02	43	1	47	2
	30	1.35	0.15	4.43	0.20	64	8	0.96	0.60	0.40	0.16	2.20	0.34	7.32	0.02	43	1	43	2
	40	1.03	0.08	4.31	0.23	56	5	1.21	0.88	0.62	0.24	3.05	0.67	7.28	0.02	40	1	38	2
Halothane	0	3.61	0.19	6.58	0.12	92	2	0.81	0.26	0.11	0.06	2.57	0.33	7.32	0.01	42	1	59	2
	10	2.64	0.16	5.82	0.20	85	4	0.80	0.27	0.17	0.06	2.47	0.39	7.33	0.01	43	1	53	1
	20	2.16	0.25	5.88	0.22	77	3	0.89	0.26	0.22*	0.06	2.59	0.45	7.33	0.01	43	1	47	2
	30	1.74	0.21	5.45	0.32	67	7	0.92	0.27	0.25*	0.07	2.51	0.58	7.32	0.01	42	1	45	3
	40	1.35	0.17	5.11	0.35	61	8	1.41	0.29	0.56	0.23	3.02	0.87	7.31	0.01	42	1	39	3

* Significantly greater ($P < 0.05$) than 0 blood loss value by Student's t-test, paired data.
† Four dogs in this group.

sive reduction in numbers of animals in both C_3H_6 groups, which rendered comparative responses less meaningful. For either C_3H_6 group as compared with either the isoflurane or halothane group, MAP was greater initially and $P\bar{v}_{O_2}$'s, which reflect the overall relationship between $\dot{Q}$ and $\dot{V}_{O_2}$, were similar. With blood loss, MAP, $\dot{Q}$, and $P\bar{v}_{O_2}$ were well maintained early in either C_3H_6 group but eventually decreased to a greater extent than with either isoflurane or halothane. These changes were accompanied in the C_3H_6 groups by the earlier appearance of increased concentrations of E and L and lesser *p*H and BB values at a total loss of 40 ml/kg.

The hemodynamic observations for individual dogs in the C_3H_6/SCh and halothane groups are displayed in figures 2 and 3. The findings in these groups were selected for comparison on the basis of representation of the extremes of the range of responses. In addition to emphasizing the prolonged survival and better maintenance of hemodynamics at comparable degrees of blood removal with halothane, these observations illustrate that in both groups when death occurred the cardiac outputs were similar, and also that in the C_3H_6/SCh group this output was reached earlier and in association with a higher MAP.

Although these hemodynamic and metabolic responses were qualitatively similar to those previously observed, the actual concentrations of E and L in the present study were less.[2] One possible explanation of this was that this finding reflected a systemic difference between results obtained by the total catecholamine method of the previous study and the current, more sophisticated E and N analysis; this possibility, however, was excluded by obtaining satisfactory agreement between results obtained for duplicate samples by the two methods. Another possibility was that the difference was related to a shorter time interval between blood removal steps in the present (10 ml/kg/30 min) as compared with the previous (10 ml/kg/60 min) study. Since significantly increased concentrations of E and L are uncommon prior to a blood loss of 30 to 40 ml/kg, a pilot study was carried out to determine the influence of time alone on E and L concentrations after a single-step blood removal of

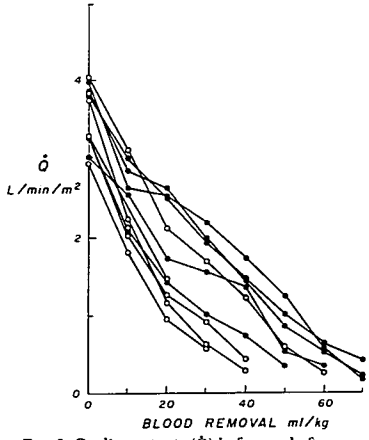

FIG. 2. Cardiac outputs ($\dot{Q}$) before and after progressive bleeding (10 ml/kg/30 min) in individual dogs during anesthesia with either C_3H_6/SCh (open circles) or halothane (closed circles).

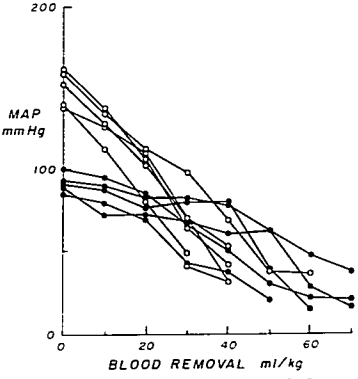

FIG. 3. Mean arterial pressures (MAP) before and after progressive bleeding (10 ml/kg/30 min) in individual dogs during anesthesia with either C_3H_6/SCh (open circles) or halothane (closed circles).

35 ml/kg. With C_3H_6/SCh, this resulted in progressive, parallel increases in E and L; concentrations of both surpassed those observed at even greater total blood-removal

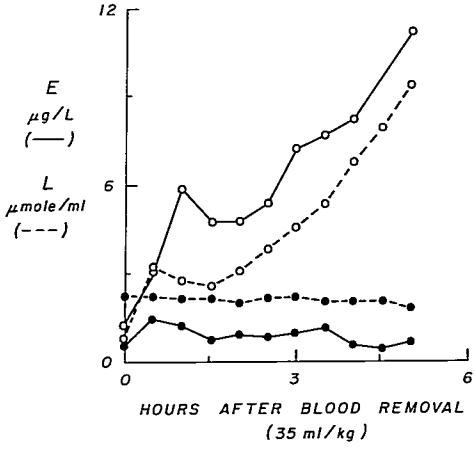

FIG. 4. Arterial concentrations of epinephrine (solid lines) and lactate (dashed lines) at different times after removal of 35 ml/kg blood during anesthesia with either C_3H_6/SCh (open circles) or halothane (closed circles) (one dog each).

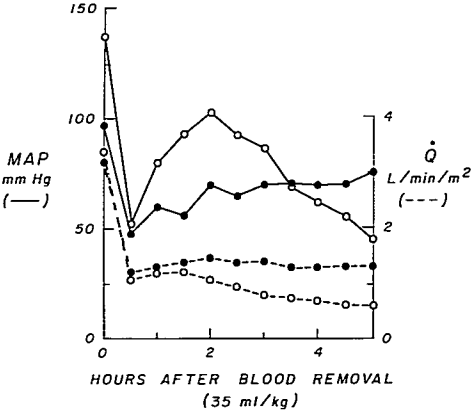

FIG. 5. Mean arterial pressures (MAP) and cardiac outputs ($\dot{Q}$) at different times after removal of 35 ml/kg blood during anesthesia with either C_3H_6/SCh (open circles) or halothane (closed circles) (one dog each).

values in the incremental studies (fig. 4). In this situation, hemodynamic functions deteriorated progressively, and death occurred 5 hours after blood removal (fig. 5). With halothane, the concentrations of E and L did not change significantly with blood removal or passage of time, and hemodynamic values stabilized at a new level of MAP and $\dot{Q}$ without evidence of deterioration (figs. 4 and 5). These findings clearly suggest that, after blood removal, time and the anesthetic drug have important influences on E and L concentrations.

Although increased concentrations of E and L clearly were involved in these differences in responses to unreplaced blood loss, the individual effect of each could not be ascertained from the blood-removal studies

TABLE 2. Response to Lactic Acid Infusion (Five Dogs Each, 37 C, C_3H_6/SCh)

Variable	Lactic Acid Infused (mEq/30 Min; Mean ± SE)					
	None		136 ± 24		187 ± 16	
Arterial lactate, μmol/ml	3.54	0.33	6.96	0.26	10.51	0.46
Epinephrine, μg/l	1.13	0.18	0.82	0.05	0.95	0.10
Norepinephrine, μg/l	0.20	0.03	0.20	0.04	0.26	0.04
*p*H	7.28	0.02	7.16	0.01	6.98	0.03
Buffer base, mEq/l	39	1	31	1	24	1
Arterial pressure, mean, mm Hg	135	11	138	10	129	10
Q, l/min/m²	3.31	0.37	2.81	0.47	2.58	0.52
$\dot{V}_{O_2}$, ml/min/kg	6.39	0.31	6.59	0.50	6.63	0.65

alone. In each group, E and L concentrations were directly related, and this relationship was not significantly different between groups. The regression equation calculated by the method of least squares from all observations was

$$L\ (\mu mol/ml) = 2.66 + 0.41 \pm 0.03\ E\ (\mu g/l).$$

Because it was conceivable that the chain of events could involve either an increased E concentration leading to an increased L concentration or *vice versa*, infusion studies were performed in the absence of unreplaced blood loss. In the first of these, two levels of lactic acidemia were created by appropriate intravenous infusions of lactic acid. The degrees of lactic acidemia extended beyond the range of L concentrations observed in the blood-removal studies and resulted in neither increased concentrations of E or N nor deterioration of hemodynamic or metabolic values (table 2). Accordingly, it was concluded that the increase in E concentration in the blood-removal studies was not secondary to an increased concentration of L and that the increase in L concentration—conceivably an indication of deterioration—was not the cause of death.

The converse of this question—whether increased concentrations of E, N, or E plus N result in increased L concentrations—was examined in six additional infusion studies during anesthesia with either C_3H_6/SCh or isoflurane. Isoflurane was used for this comparative study rather than halothane in order to lessen the possibility of inducing arrhythmias with infusion of E.[8] Infusion of N alone in amounts sufficient to increase the concentration to the extent observed in the blood-removal studies did not result in an increased L concentration (table 3). Infusion of E alone did result in an increased L concentration and, overall, the relationship between E and L concentrations created by infusion of E was direct, significant, and not different from that observed in the blood-removal studies. The response of L to infusion of E plus N was not significantly different from that with E alone. The regression equation calculated from all observations in these infusion studies was

$$L\ (\mu mol/ml) = 3.84 + 0.32 \pm 0.06\ E\ (\mu g/l).$$

This relationship between L and E was not significantly different from that established in the blood-removal studies (fig. 6). $\dot{Q}$, $\dot{V}_{O_2}$, and MAP were determined in all of these studies, but they are tabulated only for the studies wherein E plus N was infused, for the sake of both brevity and cogency (table 3). Although extensive analysis of these observations is limited by the fact that only one dog was studied in each circumstance, the data do suggest that elevated concentrations of E, N, and L will not by themselves lead to the hemodynamic and metabolic deterioration occurring when these concentrations exist in conjunction with hypovolemia.

Discussion

In 1961, Smith and associates[5] claimed, on the basis of clinical and laboratory observations, that hypovolemia was tolerated better during halothane than during cyclopropane anesthesia. This claim challenged the traditional view developed by Hershey and associates[3] that C_3H_8 was, by virtue of its salutary effects on the microcirculation, a nearly ideal agent for the management of

cases of hemorrhagic shock. This position was also supported by Price and associates,[4] who stated that their findings with C_3H_6 ". . . agree well with the clinical impression, that cyclopropane is the anesthetic agent of choice in the presence of hemorrhagic and traumatic shock." This conclusion was based on the demonstration in man that C_3H_6, as compared with halothane, results in increased sympathetic nervous system reactivity and better preservation of arterial blood pressure and heart rate.

To some extent, these divergent views are the result of applying different yardsticks to different experimental models. Smith and associates[5] based their unfavorable view of C_3H_6 on survival studies in dogs in which the blood volume was severely depleted (as much as 50 per cent) and on responses in severely injured patients. Hershey and associates[3] based their favorable view of C_3H_6 on microcirculatory studies in animals in which blood loss had been ". . . as high as 4%" and some clinical studies of responsiveness to blood transfusion therapy. Price and associates[4] arrived at their favorable impression from observations obtained prior to minor elective surgical procedures in otherwise normal patients.

The present study is an extension of the type of study initiated by Smith and associates.[5] Our findings substantiate and expand those of Smith and associates. The anesthetic agents were selected to provide a range of sympathoadrenal reactivity, C_3H_6/SCh offering the greatest range and isoflurane and halothane the least.[9,10] Average survival times correlated inversely with the relative sympathoadrenal reactivity associated with the particular agent and lesser survival times were associated with the earlier appearance of increased concentrations of E and L.

The use of plasma concentrations of E and N as indices of sympathoadrenal activity in studies of this type is regarded by others as most appropriate.[11] In the blood removal studies, E and L concentrations were directly related and infusion studies suggested that an increase in the concentration of E was the precursor of an increase in the concentration of L. In the absence of hypovolemia, however, establishment of increased concentrations of E and L did not result in the hemodynamic and metabolic deterioration seen in the blood-removal studies. Such deterioration was dependent not only on the anesthetic agent and the total blood loss but also on the mere passage of time in the absence of further blood removal.

These findings are compatible with current concepts of the potential role of the sympathoadrenal system in response to hemorrhage. Taken together, they suggest the following hypothesis. With minor degrees of hypovolemia and activation of the sympathoadrenal system, the combined effects of epinephrine and norepinephrine tend to maintain arterial blood pressure by constrictor effects on certain precapillary sphincters. These effects increase the total peripheral vascular resistance and positive inotropic and chronotropic cardiac activity which, in turn, lessens the decrease

TABLE 3. Epinephrine (E), Norepinephrine (N), and Lactate in Individual Dogs before and with of E + N during Anesthesia with Cyclo-

	Infusion	Epinephrine (μg/l)	Norepinephrine (μg/l)	Lactate (μM/ml)	Infusion	Epinephrine (μg/l)	Norepinephrine (μg/l)	Lactate (μM/ml)
C_3H_6/SCh	0	1.4	0.3	3.8	0	0.5	0.2	3.7
	Norepinephrine	1.8	0.7	3.1	Epinephrine	1.4	0.2	4.2
	Norepinephrine	1.8	0.8	2.7	Epinephrine	2.4	0.2	5.0
	Norepinephrine	1.7	0.8	2.7	Epinephrine	3.4	0.2	5.6
	Norepinephrine	1.7	1.8	2.7	Epinephrine	3.5	0.4	6.2
	Norepinephrine	2.0	4.2	2.6	Epinephrine	12.8	0.5	6.8
Isoflurane	0	0.4	0.1	0.7	Epinephrine	1.0	0.3	2.6
	Norepinephrine	0.4	0.2	0.9	Epinephrine	2.0	0.3	3.2
	Norepinephrine	0.4	0.3	0.5	Epinephrine	1.4	0.4	3.6
	Norepinephrine	0.3	0.7	0.3	Epinephrine	4.1	0.1	4.8
	Norepinephrine	0.2	1.2	0.3	Epinephrine	7.4	0.3	5.8
	Norepinephrine	0.1	2.5	0.6	Epinephrine	12.6	0.1	7.1

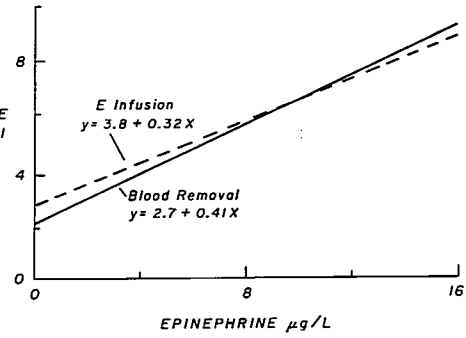

FIG. 6. Comparison of relationship between blood lactate and plasma epinephrine for all observations in blood-removal studies (solid line) and infusion studies (dashed line).

in cardiac output occasioned by the reduction in filling pressure.[1] The major sites of increased resistance and reduced blood flow are presumably skin, muscle, and kidney, and there are no known unfavorable sequelae of minor reductions in blood flow to these tissues. It can be argued that such a response is desirable in that cerebral, coronary, and splanchnic blood flow are thus preserved and that blood volume restoration rapidly causes blood to flow again in the temporarily ischemic tissues. Although this response is unquestionably important in the survival of the wounded man distant from medical intervention, it would appear to be less important for an anesthetized surgical patient in whom hypovolemia would tend to be concealed.

With major hypovolemia and activation of the sympathoadrenal system, the developing pattern is one of early maintenance of arterial blood pressure, based almost entirely on increase in peripheral vascular resistance, but late decline of pressure and deterioration of cardiac output (fig. 5). The exact mechanisms responsible for this pattern have not been elucidated by the present study and are not known to us. Possibilities include deleterious effects of the lactic acidemia on myocardial and other organ functions, hypoxic deterioration and disorganization of the microcirculation, and *in-vivo* decreased circulating blood volume, with sludging and stagnation of blood in slowly perfused capillary beds.

Irving[6] reached similar conclusions from a series of studies in which a different approach was used. His findings are worth reviewing.

Infusion of E, N, or E + N, and Cardiac Output, O_2 Uptake, and Mean Arterial Pressure with Infusion propane (and Succinylcholine) or Isoflurane

Infusion	Epinephrine (μg/l)	Norepinephrine (μg/l)	Lactate (μM/ml)	Cardiac Output (l/min/m²)	O_2 Uptake (ml/min/kg)	Mean Arterial Pressure (mm Hg)
0	0.8	0.1	4.9	5.6	7.1	116
Norepinephrine + epinephrine	1.2	0.3	5.3	5.9	6.8	137
Norepinephrine + epinephrine	2.3	0.5	6.1	5.0	6.3	130
Norepinephrine + epinephrine	2.8	0.5	6.7	5.9	8.1	120
Norepinephrine + epinephrine	6.7	0.7	7.5	4.3	6.7	129
Norepinephrine + epinephrine	13.0	1.4	7.6	4.6	8.0	167
Norepinephrine + epinephrine	0.5	0.1	1.2	2.7	5.8	90
Norepinephrine + epinephrine	0.8	0.4	2.5	3.8	7.3	88
Norepinephrine + epinephrine	1.4	0.4	3.9	4.5	8.2	111
Norepinephrine + epinephrine	2.9	0.6	5.6	4.1	6.7	96
Norepinephrine + epinephrine	5.2	0.7	7.0	4.2	7.8	99
Norepinephrine + epinephrine	10.9	1.9	7.9	4.8	8.4	110

Sheep and dogs, anesthetized with thiopental and bled to a fixed arterial pressure of 35 to 45 mm Hg (Lamson hydrostatic bottle), showed, with the passage of time, the picture of progressive hemodynamic and metabolic deterioration and eventual death that was associated in the present study with C_3H_8/SCh and a blood loss of 35 ml/kg. This course of events was accelerated by the administration of either metaraminol (6 to 7 μg/kg/min) or epinephrine (1.2 μg/kg/min); it was not modified by celiac ganglionectomy in animals with intact adrenal glands. Denervation of the adrenals did not improve the tolerance to hypotension but did prevent development of lactic acidosis. Neither alpha-blockade (phenoxybenzamine, 1 mg/kg) nor beta-blockade (propranolol, 7 μg/kg/min) alone improved the tolerance to hypotension. However, when both alpha blockade and beta blockade were achieved by administration of these drugs in combination, tolerance was greatly improved: all five dogs and 14 of 16 sheep treated prophylactically in this manner survived what was normally a fatal procedure. Sheep receiving an epinephrine infusion in addition were similarly protected. In these animals lactic acidemia did not occur. These beneficial effects could be achieved only by establishing blockade prior to inducing hypotension. Irving[6] emphasized not only the contributory role of sympathoadrenal factors—particularly alpha and beta receptor activity—to the irreversibility of hemorrhagic shock but also the concept that the ". . . lactic acidosis of haemorrhagic hypotension results from the action of both circulating and tissue catecholamines upon intracellular enzyme mechanisms rather than from hypoxia itself." We add our support to these views.[2-12]

The practical implications of this material seem clear. Hypovolemia and hypotension should always be avoided; when present they should be promptly corrected. When using anesthetic agents capable of enhancing sympathoadrenal activity, arterial blood pressure is an unreliable index of adequacy of blood volume, cardiac output, and tissue perfusion. With agents which suppress sympathoadrenal activity, absence of metabolic acidosis and lactic acidemia cannot be equated with adequate cardiac output, tissue blood flow, and oxygenation.

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