EFFECT OF PHENYLEPHRINE ON SURVIVAL AND ACID-BASE BALANCE IN DOGS WITH ACUTE HEMORRHAGIC HYPOTENSION

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THE value of vasopressor drugs for maintenance of blood pressure in acute hemorrhagic hypotension when blood is not immediately available remains controversial. Results of controlled laboratory studies are conflicting because of variations in methods and volumes of bleeding, anesthetic agents used, pharmacological differences between vasopressors and other innumerable factors which may influence the outcome of therapy.

Simeone *et al.*[1] gave *l*-norepinephrine to dogs bled arterially to a blood pressure of 30–40 mm. of mercury and found an 88 per cent survival compared to 35 per cent in dogs serving as controls. Sarnoff and Kaufman [2] bled dogs to mean arterial levels of 40 mm. of mercury in one hour and found a 50 per cent survival in those treated with metaraminol and 10 per cent in a control series. On the other hand, Close and his associates [3] found that when they bled dogs by graded hemorrhages over a 45 minute period and then gave *l*-norepinephrine they had a 62 per cent mortality rate. In another series when *l*-norepinephrine was given during bleeding to maintain blood pressure at 90 mm. of mercury the mortality rate remained unchanged. A control series of dogs had a 33 per cent mortality.

The purposes of this study were: 1) to determine the survival rates of dogs on constant volume ventilation when subjected to acute hemorrhagic hypotension and treated with phenylephrine to raise and maintain their blood pressure; 2) to observe the effects of phenylephrine on preventing or correcting acidosis which accompanies hemorrhagic hypotension.

METHOD

Forty nonfasting mongrel dogs weighing 9–18 kg. were anesthetized with pentobarbital 25 mg./kg. and given gallamine triethiodide for muscular relaxation. The animals' lungs were ventilated with a constant-volume respirator (Palmer Ideal Pump) with sufficient volumes of a 30 per cent oxygen-70 per cent nitrogen gas mixture to maintain a "steady state" and an end-tidal P_{CO_2} of 35–40 mm. of mercury. After a stabilization period of 30–60 minutes the animals were bled by means of a catheter in the aorta, within a period of five minutes, to a mean pressure of 40 mm. of mercury. The dogs were observed for five minutes after which phenylephrine was administered intravenously to raise and maintain blood pressure at 120 mm. of mercury or over for 30 minutes. The pronounced difference in mortality rates of the phenylephrine treated and control groups led to investigation of another series of dogs in which the blood pressure was elevated with phenylephrine and then maintained at 70–80 mm. of mercury. This pressure was selected because it approximates levels most generally believed necessary to maintain adequate blood flows to essential organs of the body. After administration of the vasopressor for 30 minutes following hemorrhage the drugs were discontinued and the animals allowed to further adjust to the hemorrhage without additional therapy. Animals in the control group were treated similarily except for the omission of phenylephrine. All surgical procedures were done with aseptic technique.

End-tidal and minute volume carbon dioxide output measurements and arterial and venous blood *p*H determinations were made at intervals throughout the course of the experiment. Samples of mixed venous blood were drawn from a catheter in the right atrium; arterial blood samples were taken from the abdominal aorta. Carbon dioxide was measured with a Beckman Model LBI Analyzer, and ventilatory volumes were determined with a Monaghan Ventilation Meter. Blood *p*H was determined by the method of Severinghaus *et al.*[4] with a Cambridge Research Model *p*H Meter keeping the glass electrode at 37 C.

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TABLE 1

MORTALITY RATES AND BLEEDING VOLUMES OF CONTROL AND PHENYLEPHRINE-TREATED GROUPS

Bleeding Volumes ml./kg.	Survived
Control Group	
32	yes
24	yes
39	yes
27	yes
30	yes
45	yes
39	yes
44	yes
27	yes
35	yes
40	no
$\bar{X}$ 34.7	Total Dogs 11
S.D. 7.30	Died 1
S.E. 2.30	Mortality 9%
Group A(s)	
29	yes
35	yes
34	yes
45	yes
38	yes
22	yes
40	yes
$\bar{X}$ 34.7	
S.D. 7.51	
S.E. 2.84	
Group A(d)	
30	no
30	no
45	no
46	no
39	no
46	no
41	no
38	no
35	no
$\bar{X}$ 38.8	Total Dogs 16
S.D. 6.27	Died 9
S.E. 2.09	Mortality 59%
Group B	
25	yes
31	yes
29	yes
33	yes
32	yes
45	yes
36	yes
41	yes
$\bar{X}$ 35.2	Total Dogs 8
S.D. 6.76	Died 0
S.E. 2.38	Mortality 0%

$\bar{X}$ = Mean of group.
S.D. = Mean standard deviation.
S.E. = Standard error of mean.

Mean blood pressure was recorded by means of a catheter in the aorta at the level of the diaphragm with a dampened mercury manometer. Body temperatures were monitored continuously with a Yellow Springs Telethermometer. Attempts at maintaining constant body temperatures by use of a water mattress were largely unsuccessful and variations of 2 to 3 degrees centigrade often occurred during the experiment.

RESULTS

For purposes of analysis, our results are divided as follows: Group A includes those animals receiving phenylephrine to maintain blood pressure at 120 mm. Hg. or over for 30 minutes; this was sub-divided into Group A (s) and Group A (d) depending on whether the animals survived or died. The dogs in Group B received phenylephrine to maintain their blood pressure at 70–80 mm. of mercury for 30 minutes. The control group was treated in a similar manner except that vasopressors were omitted.

A. Bleeding Volumes. When blood pressure is used as an end point for cessation of hemorrhage, it is necessary to compare the amounts of blood removed. The number of milliliters of blood removed from each dog on a per kilogram body weight basis is listed in table 1. While Group A (d) had 3 to 4 ml./kg. more blood removed than the other groups, on statistical analysis using the Student "t" test, this difference is not significant ($p = > .2$).

B. Mortality Rates. Table 1 also shows the number of animals in each group which died. Six of the dogs in the phenylephrine-treated group died within four hours after bleeding; two others died the night of the experiment; and the other two died within 48 hours. The animals which died after four hours responded poorly to stimuli, could not stand erect, and would not eat or drink.

C. Arterial and Venous Blood pH. After hemorrhage the animals became acidotic (table 2 and fig. 1). Thirty minutes after hemorrhage the Control Group and Group B were no more acidotic than five minutes after hemorrhage. Group A (s) arterial pH samples were significantly lower ($p = < .05$); however, venous differences were not. Group A (d) animals were definitely more acidotic ($p = < .01$).

TABLE 2

*p*H Values of Arterial–Venous Blood Before and After Hemorrhage and Following Phenylephrine Administration

Control Group						Group A Treated (Survived)					
Pre-Hemorrhage		5 min. after		30 min. after		Pre-Hemorrhage		5 min. after		30 min. after	
Art.	Ven.	Art.	Ven.	Art.	Ven.	Art.	Ven.	Art.	Ven.	Art.	Ven.
7.33	7.32	7.27	7.26	7.19	7.14	7.33	7.30	7.26	7.23	7.26	7.20
7.35	7.32	7.32	7.26	7.36	7.34	7.31	7.30	7.28	7.18	7.26	7.21
7.35	7.32	7.31	7.25	7.25	7.20	7.36	7.33	7.32	7.30	7.26	7.09
7.33	7.31	7.30	7.28	7.26	7.23	7.36	7.32	7.30	7.24	7.13	7.13
7.38	7.36	7.33	7.13	7.25	7.16	7.36	7.32	7.26	7.18	7.14	7.13
7.37	7.34	7.35	7.21	7.25	7.13	7.42	7.38	7.40	7.33	7.23	7.21
7.38	7.36	7.33	7.17	7.31	7.23	7.40	7.37	7.32	7.19	7.23	7.16
7.42	7.40	7.42	7.30	7.28	7.24						
7.34	7.32	7.26	7.20	7.24	7.16						
7.36	7.33	7.26	7.23	7.29	7.26						
X 7.36	7.34	7.31	7.25	7.27	7.23	X 7.36	7.34	7.30	7.23	7.23	7.21
±.0278	.0235	.0648	.0581	.0382	.0645	±.0374	.0333	.0510	.0613	.0590	.0707
p =		<.02	<.001	>.05	<.5	*p* =		<.05	<.001	<.05	<.7

Group A Treated (Died)						Group B Treated					
Pre-Hemorrhage		5 min. after		30 min. after		Pre-Hemorrhage		5 min. after		30 min. after	
Art.	Ven.	Art.	Ven.	Art.	Ven.	Art.	Ven.	Art.	Ven.	Art.	Ven.
7.35	7.32			7.08	7.03	7.36	7.36	7.29	7.20	7.20	7.20
7.36	7.33	7.36	7.33	7.23	7.20	7.37	7.36	7.27	7.22	7.32	7.27
7.33	7.32	7.23	7.23	7.15	7.13	7.38	7.36	7.26	7.19	7.27	7.24
7.33	7.30			7.08	6.93	7.37	7.34	7.33	7.28	7.30	7.26
7.30	7.38	7.26	7.14	7.20	7.13	7.42	7.39	7.23	7.19	7.27	7.20
7.41	7.38	7.30	7.21	7.28	7.19	7.39	7.35	7.30	7.27	7.22	7.18
7.40	7.37	7.37	7.30	7.26	7.24	7.40	7.39	7.26	7.21	7.32	7.30
7.38	7.36	7.38	7.24	7.22	7.17	7.39	7.32	7.22	7.17	7.26	7.20
7.36	7.33	7.26	7.23	7.11	7.08						
X 7.36	7.34	7.31	7.24	7.17	7.12	X 7.38	7.36	7.26	7.21	7.26	7.23
±.0353	.028	.067	.0618	.077	.0958	±.0227	.0236	.0377	.0398	.0447	.0448
p =		>.05	<.01	<.01	<.02	*p* =		<.001	<.001		

$\bar{X}$ = Mean of group.
± = Mean standard deviation.
p = Value from Student "t" test.

Comparing the four Groups, Group A (s), Group B and the Control Group were not found to differ after phenylephrine; however, Group B and the Control Group were less acidotic than Group A (d). The mean *p*H of the arterial blood of Group A (s) and A (d) were 7.23 and 7.17, respectively, but the difference was not statistically significant ($p = > .05$). When the Control Group was compared with the entire Group A, the difference was significant; Group A animals had a lower blood *p*H (Arterial $p = < .01$, venous $p = < .05$).

D. Dosages of Phenylephrine. Dogs in Group A (d) were found to have received an average of .42 mg./kg. to maintain their blood pressure above 120 as compared to .22 mg./kg. for Group A (s). This difference was not quite statistically significant. ($p = > .05$). However, when Group A was compared with Group B the difference was highly significant, .338 mg./kg. and .034 mg./kg. respectively ($p = < .001$).

E. Carbon Dioxide Output. Expired carbon dioxide and end-tidal P_{CO_2} fell during hemorrhage. Concomitant with the rise in blood pressure following phenylephrine, there was a prompt rise in carbon dioxide output. Minute volume carbon dioxide output was corrected to STSP and is expressed in figure 2 as per cent of pre-hemorrhage values. Fifteen minutes after the observation period all the phenylephrine treated groups had statistically significantly higher total carbon dioxide outputs than the control group (A (s) < .001, A (d) < .025, B < .05). Thirty minutes after

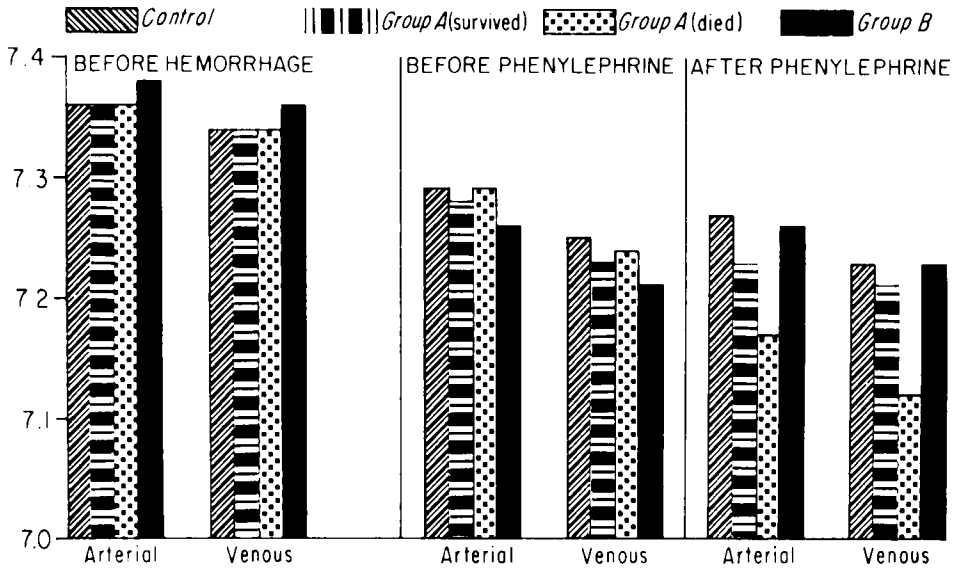

FIG. 1. Comparison of *p*H values of arterial and venous blood before hemorrhage, 5 minutes after hemorrhage (before phenylephrine) and following phenylephrine administration.

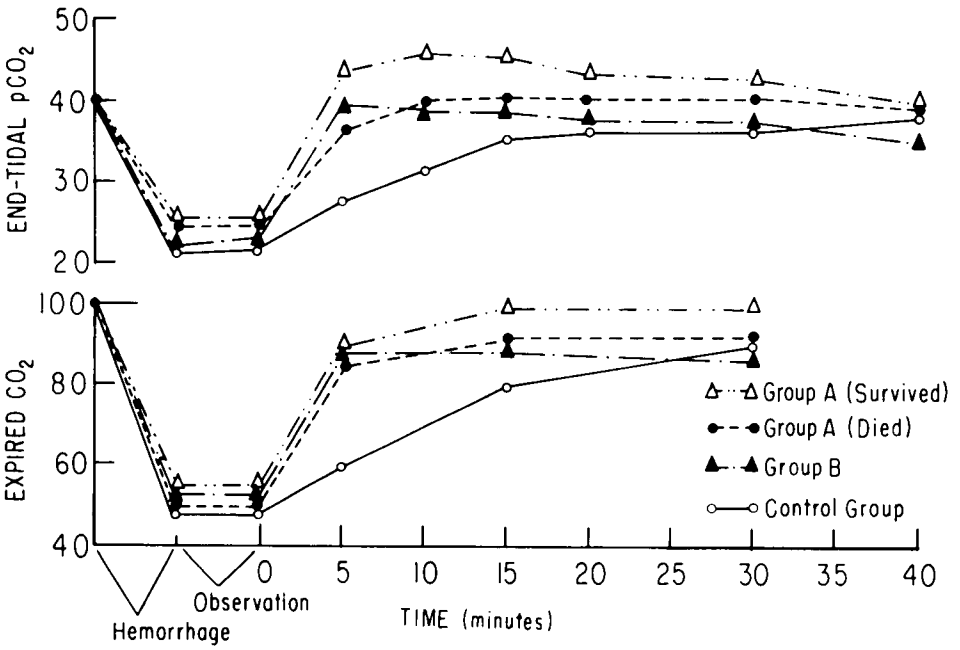

FIG. 2. End-tidal P_{CO_2} and expired CO_2 values of phenylephrine-treated and control groups. Expired CO_2 is expressed as per cent of pre-hemorrhage values.

TABLE 3

END-TIDAL P_{CO_2} IN MM./HG AND EXPIRED CO_2 IN ML./MIN. ARE GIVEN FOR ALL GROUPS. DATA ARE PRESENTED AS MEAN OF THE GROUP AND RANGE

Group	Pre-Hemorrhage	Post-Hemorrhage	Observ.	(Min.) 5	(Min.) 10	(Min.) 15	(Min.) 20	(Min.) 30	(Min.) 40
Control	40.7 37–42	21.7 25–29	23.2 15–29	27.6 16–36	31.0 26–38	36.1 29–42	36.0 33–44	36.0 33–62	39.0 23–50
A (Survived)	40.7 38–41	25.5 21–28	25.3 19–29	44.0 32–48	46.0 35–37	45.7 22–48	44.9 36–51	43.0 36–59	40.0 34–57
A (Died)	41.3 38–45	22.2 15–29	22.8 15–27	36.0 25–48	40.0 22–56	40.3 35–56	40.4 22–48	40.5 23–62	39.0 22–48
B	39.7 38–40	25.0 18–28	25.6 21–30	39.0 34–48	38.0 28–56	37.0 29–45	36.5 28–44	37.3 29–51	35.0 33–51
				EXPIRED CO_2					
Control	68.1 30–110	—	34.8 16–57 *49%	41.5 20–69 60%	—	52.8 25–88 79%	—	62.1 29–100 90%	—
A (Survived)	73.5 32–100	—	41.1 17–59 55%	66.0 31–96 90%	—	72.8 31–100 99%	—	73.8 33–103 100%	—
A (Died)	76.1 53–99	—	38.1 28–59 50%	63.0 43–106 85%	—	66.0 48–96 91%	—	74.3 42–103 91%	—
B	87.0 59–107	—	46.0 33–56 54%	75.2 49–95 88%	—	77.6 51–100 89%	—	76.0 51–92 87%	—

* Expired CO_2 expressed as per cent of pre-hemorrhage values.

the observation period at the termination of phenylephrine therapy all groups were alike with the exception of Group A (s) which maintained a higher carbon dioxide output. End-tidal P_{CO_2} paralleled minute volume carbon dioxide output and ten minutes after cessation of phenylephrine was alike for all groups.

F. Duration of Hypotension of the Control Group. The mean duration of hypotension of dogs in the Control Group was 37 minutes with a range of 18–80 minutes. A blood pressure of 70 mm. of mercury was considered as terminating the hypotensive period.

DISCUSSION

Results of these experiments indicate that doses of phenylephrine necessary to return and maintain blood pressure of hemorrhaged dogs to pre-existing levels were injurious to a significant number of animals. On the other hand, allowing the animals to adjust to hemorrhage without treatment or maintaining blood pressure at 70–80 mm. of mercury with phenylephrine did not prove to be detrimental. Blood pressure maintenance at pre-existing levels necessitated giving repeated doses or at times continuous drug therapy. If the lower levels of blood pressure were tolerated only small doses or, in several instances, a single dose was sufficient.

The metabolic acidosis following hemorrhage [5, 6] might be expected to improve with administration of phenylephrine and return of carbon dioxide output to normal levels. This improvement did not occur, for the phenylephrine treated animals were either more acidotic (Group A) or they continued with the same degree of acidosis (Group B). These

findings suggest that the degree of metabolic acidosis had increased, that vasoconstriction caused a diminution of blood flow to tissues leading to a greater degree of hypoxemia and thereby higher fixed-acid concentrations in the blood. An increase in metabolism could also account for a higher carbon dioxide output and a lower blood *p*H. We have observed, however, in other experiments that carbon dioxide output did not rise when phenylephrine was given to normal dogs and concluded that the drug does not increase metabolic rate. Horvath and Knapp [7] failed to observe a change in oxygen consumption after phenylephrine. *l*-Norepinephrine, on the other hand, enhances metabolism if large amounts are given; [8] doses which may be necessary to raise the blood pressure of severely hemorrhaged dogs. Other workers have found diminished pressor responses to sympathomimetic amines in animals with low blood *p*H values which may necessitate employing larger doses.[9, 10] An increase in metabolic rate in tissues having a diminished blood flow would theoretically be undesirable and for this reason phenylephrine was used in our experiments.

Gerst, Rattenborg, and Holaday [5] found an arterial to end-tidal carbon dioxide tension difference during hemorrhagic hypotension signifying ventilated but not perfused alveoli, thereby increasing physiological (alveolar) dead space. Upon re-infusion of blood, this carbon dioxide tension difference was corrected, indicating that alveoli were again perfused, resulting in less respiratory dead space.

In our studies explanation is lacking for the rise in carbon dioxide output and apparent improvement in pulmonary circulation following phenylephrine. A most likely cause for the marked rise in carbon dioxide output is from an increased venous return to the heart and an increased cardiac output. The greater volume of blood in the pulmonary circulation possibly with higher pressure re-opened alveoli which were not perfused during the hypotensive period. Perfusion of more alveoli reduced physiological dead space which resulted in an elevation of carbon dioxide output.

Acidosis following severe hemorrhage is corrected with re-infusion of blood and improvement of carbon dioxide elimination.[5] However, acidosis following hemorrhage in the animals in this study was not corrected by elevation of the blood pressure with phenylephrine, although there was a definite increase in carbon dioxide output. Improvement in carbon dioxide output by phenylephrine administration following hemorrhage bears no relationship to survival of the animals as shown in this study.

Summary

1. Dogs with constant volume pulmonary ventilation subjected to hemorrhage sufficient to reduce arterial blood pressure to 40 mm. of mercury survived when allowed to adjust without therapy, or when treated with phenylephrine to raise their blood pressure and then maintain the blood pressure at 70–80 mm. of mercury. Treatment of hemorrhaged dogs with phenylephrine to maintain blood pressure at 120 mm. of mercury or above resulted in death of 59 per cent of the animals.

2. Raising blood pressure with phenylephrine following hemorrhage was accompanied by a concommitant rise in end-tidal P_{CO_2} and total carbon dioxide output, whereas, untreated dogs required an average of 20 minutes to attain similar levels. Despite greater carbon dioxide output in animals maintained at pre-existing blood pressures, they become more acidotic than untreated animals or those maintained at lower blood pressures.

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EPIDURAL BLOCK IN ECLAMPSIA It is generally agreed that the hypertension of eclampsia can be controlled adequately by continuous spinal sympathetic nerve block. The method provides a more alert, cooperative patient free from the pain of uterine contractions, and reduces or eliminated further convulsive episodes. There is a reduction in the danger of maternal respiratory morbidity and fetal anoxia from heavy sedation. In addition, the patient can be delivered by either the vaginal or abdominal route, as adequate anesthesia is available as required. (*Mylks, G., and others: Acute Fulminating Eclampsia—Management in Conjunction with Prolonged Epidural Sympathetic Block, Canad. M. A. J. 82: 422 (Feb. 20) 1960.*)

PETHIDINE-ANTAGONIST MIXTURES One hundred and thirty primigravid parturients were treated with a mixture of 100 mg. pethidine to 2 mg. of levallorphan for labor pain. The mean dosage was 242 mg. of pethidine. The initial injection was given at two fingerbreadths' cervical dilatation. Gas-air or "trilene"-air was used for delivery. Analgesia was good in 76 per cent, fair in 21 per cent and absent in three per cent. Of 48 patients questioned, 60 per cent thought the mixture provided more analgesia than gas-air. Eighty-nine per cent of the babies cried within one minute and none required vigorous resuscitation. There was no increase in infant morbidity or mortality, no prolongation of labor and no increased incidence of operative deliveries or postpartum hemorrhage. The series compares favorably with those in which mixtures of pethidine and nalorphine were used except that nalorphine appears to provide better amnesia. Forty per cent more pethidine was used than in the pethidine alone series. The dosage of levallorphan is perhaps too great. (*Bullough, J.: Use of Premixed Pethidine and Antagonists in Obstetrical Analgesia, Brit. Med. J. 2: 859 (Oct. 31) 1959.*)