Hidden Hypercapnia in Hemorrhagic Hypotension

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In hemorrhagic shock with normal or reduced $P_{A_{CO_2}}$, the mixed venous blood was severely hypercapnic. The shock-induced rise in the arteriovenous P_{CO_2} gradient was unaffected by hyperventilation and inversely related to blood flow. Since the acid–base composition of the extracellular fluid is likely to be closer to that of venous blood than to that of arterial blood, the authors conclude that in hemorrhagic shock metabolic and respiratory components are equally important in producing tissue acidosis. Combined blockade of the α- and β-adrenergic receptors in hemorrhagic shock suppressed both lactic acid formation and CO_2 production and significantly reduced the arteriovenous P_{CO_2} and pH gradients. (Key words: Combined adrenergic reception blockade; Hyperventilation; Metabolic acidosis; Venous blood gases; Venous blood acid–base composition.)

METABOLIC ACIDOSIS mitigated by respiratory compensation is considered a typical response to hemorrhagic shock.[1] Studies of arterial blood form the usual basis of this assumption, although it is understood that the acid–base composition of extracellular fluid is closer to that of mixed venous blood. However, normally, the gradient between $P_{A_{CO_2}}$ and $P\bar{v}_{CO_2}$ and hydrogen ion activity ($/H^+/$) is small and predictable[2] and that for lactic acid is virtually absent.[3] It is tacitly assumed that this relationship remains unaffected in shock states.

CO_2 is stored in the body in two main compartments: the alveolar–arterial compartment, equilibrated at alveolar P_{CO_2}, and the peripheral stores, in which the prevailing P_{CO_2} is that of the mixed venous blood.[4] Reduction in blood flow restricts the exposure between the two compartments and, subject to tissue CO_2 production, the gradient between $P_{A_{CO_2}}$ and $P\bar{v}_{CO_2}$ increases.[4,5,6] Theoretically, such a situation is expected to occur in shock, yet available data are few and contradictory. Arteriovenous P_{CO_2} and *p*H differences have been reported to be normal in clinical shock[7] and were considerably increased in bled dogs.[8] It appeared of interest, therefore, to examine the reliability of the arterial blood in reflecting the nature of extracellular acid–base disturbances in various stages of hemorrhagic shock.

It has been claimed that hyperventilation, if begun in the pre-bleeding period, somewhat improves the survival rate in hemorrhagic shock,[9] but in the absence of circulatory measurements the explanation has remained tentative. While circulation is not grossly depressed, hyperventilation may deplete the peripheral CO_2 stores, and we wondered if this would reduce subsequent extracellular acidosis, thus accounting for the better survival rate.

Simultaneous blockade of α- and β-adrenergic receptors reduces lactic acidosis and improves tolerance to hemorrhage.[10, 11, 12] It appeared logical to assume that this treatment would also affect extracellular acid–base composition. In this paper we report a study we undertook to substantiate this assumption.

Methods

MATERIAL

Eighteen greyhounds weighing 23 to 31 kg were used. The fasting supine animals were anesthetized with 15 mg/kg of thiopental, injected intravenously, followed by a continuous intravenous infusion of 0.20 mg/kg/min thiopental. After bleeding had commenced the dose could be considerably reduced, or even suspended, without the animals' regaining consciousness. A cuffed Magill tube was introduced into the trachea and both femoral

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arteries and veins were exposed. Repeated doses of 2 mg/kg of heparin were administered. A thermistor probe was introduced into the inferior vena cava and temperature was monitored continuously with an electric thermometer.

A cardiac catheter was passed via the femoral vein under fluoroscopic guidance into the pulmonary artery. Polyethylene tubes were inserted into the femoral arteries, and one was connected to a large siliconized reservoir.

Measurements

Oxygen saturation of arterial and mixed venous blood was measured with a Haemoreflector (Kipp and Zonen, Delft, Holland). Hemoglobin content of arterial blood was measured spectrophotometrically. Blood samples were taken simultaneously from the femoral and pulmonary arteries and analyzed immediately at 38 C for P_{CO_2}, P_{O_2} and *p*H using Radiometer (Copenhagen) microelectrodes operating through a model 22 *p*H meter (Radiometer).

Expired air was collected in Douglas bags, measured in a type E-40 wet test gas meter (Parkinson-Cowan, London), and analyzed for CO_2 concentration in a Beckman model LB-1 infrared CO_2 analyzer and for O_2 concentration in a Beckman model E-2 paramagnetic O_2 analyzer.

Femoral arterial pressure was measured with a Sanborn transducer and recorded on a Sanborn oscillograph.

Lactic acid in arterial blood[13] was measured as previously described.[11]

Calculations

The Fick principle was used to calculate cardiac output. Oxygen extraction ratio was calculated from O_2 transport (O_2 content of arterial blood x cardiac index) and O_2 uptake. Arterial and mixed venous *p*H values were converted into $/H^+/$ and expressed in mμEq/L. Gas tensions and $/H^+/$ were corrected for blood temperature using the blood-gas calculator (Radiometer, Copenhagen). All volumes and flows were expressed on the basis of body surface area (BSA). Standard statistical methods were used to analyze the results.

Groups; Protocol; Agents Used

Group A, Intact Dogs. In each of seven dogs, after control measurements (period I), the clamp was removed from the tube connecting the femoral artery with a reservoir and the dog was bled to a (mean) blood pressure of 40–60 torr, the blood being collected in the reservoir. Measurements were made at approximately 40, 90 and 170 min (periods III, IV and V, respectively). Subsequently, the shed blood was rapidly (within 10 min) reinfused, and measurements were repeated after 30 and 90 min (periods VI and VII, respectively). The trachea was then extubated, and the dog turned to its side and restrained with a canvas belt. A continuous intravenous infusion of 2 ml/min of isotonic saline solution with heparin was started and maintained until death. Most dogs remained unconscious; others were given a continuous intravenous infusion of 0.025–0.050 mg/kg/min thiopental. Arterial pressure was recorded continuously.

Group B, Hyperventilated Dogs. After control measurements each of five dogs was connected to a Bird Mark VIII respirator (Bird Corp., Palm Springs, Cal.). Air was used at pressures of +15 and −4 cm H_2O. The rate of breathing was varied to produce a wide spectrum of P_{ACO_2} levels. After an hour, as P_{ACO_2} stabilized at the desired level, measurements were made (period II) and the dog was bled into the reservoir and blood was reinfused as described above. After the first postreinfusion measurement the respirator was disconnected, and an hour later further measurements were made in the spontaneously-breathing dog. Subsequently the trachea was extubated and the saline and heparin solution was infused as described above.

Group C, Treated Dogs. An hour prior to the experiment, each of six dogs was given a slow (30 min) intravenous infusion of 1 mg/kg phenoxybenzamine (Dibenzyline, Smith, Kline and French). Twenty minutes before the experiment a continuous intravenous infusion of 4–6 μg/kg/min propranolol (Inderal, Imperial Chemical Industries) was commenced. Control measurements were followed by bleeding and reinfusion as described; after the first postreinfusion measurement (period VI) propranolol infusion was discontinued, and a

TABLE 1. Some General Effects of Hemorrhage in Intact (A) and Hyperventilated (B) Dogs and in Dogs Subjected to Combined ($\alpha + \beta$) Adrenergic Receptor Blockade (C)

	Group	Time (min)	Blood Loss ml/m²BSA	Cardiac Output (l/min/m²)	Arterial Mean Pressure (torr)	Plasma Lactate (mEq/l)
Period I, control	A			4.42(1.73)	152(19)	0.75(0.70)
	B			4.03(0.90)	158(15)	0.49(0.21)
	C			3.35(0.43)	127(24)	1.14(0.55)
Period II, control on assisted ventilation	B			4.89(1.00)	133(34)	1.39(0.61)
Period III, 40 min after commencement of bleeding	A	38(8)	1106(341)	1.12(0.35)	56(8)	2.35(1.42)
	B	49(15)	1187(306)	1.19(0.27)	49(3)	4.47(0.82)
	C	47(5)	1022(193)	1.39(0.25)	47(3)	1.45(1.06)
Period IV, 90 min after commencement of bleeding	A	86(10)	1318(305)	1.07(0.28)	51(5)	4.60(2.40)
	B	100(33)	1475(278)	1.16(0.20)	44(4)	8.06(0.90)
	C	93(10)	1257(216)	1.17(0.29)	43(4)	1.86(1.58)
Period V, 170 min after commencement of bleeding	A	177(35)	1239(296)	1.11(0.42)	49(3)	4.79(1.69)
	B	171(21)	1262(192)	1.15(0.27)	43(2)	7.88(3.54)
	C	155(15)	1230(115)	0.91(0.16)	43(3)	1.57(1.38)
Period VI, 30 min postreinfusion	A	209(21)		2.89(0.94)	113(22)	4.83(1.24)
	B	218(17)		3.02(0.57)	103(20)	8.46(4.91)
	C	200(15)		2.37(0.37)	121(12)	2.12(1.72)
Period VII, 90 min postreinfusion	A	285(57)		2.66(1.26)	113(35)	3.14(1.61)
	B	279(29)		2.25(0.66)	113(19)	4.47(4.38)
	C	289(29)		1.95(0.44)	101(18)	0.65(0.29)

further measurement was made an hour later (period VII). Subsequently the trachea was extubated and the infusion of saline and heparin solution begun. All dogs in this group remained conscious and required anesthesia.

Results

Results are shown in tables 1 and 2.

GROUP A: INTACT DOGS

Effects of Hemorrhage. Cardiac output fell to 25 per cent, and blood pressure to 30 per cent, of the control values, and both stayed at these levels during the hypovolemic phase. Lactic acid concentrations in plasma increased progressively. $P_{A_{O_2}}$ remained constant; $P_{A_{CO_2}}$ decreased (significantly in period III), $/H^+/_A$ increased progressively and was significantly ($P < 0.01$) elevated in periods IV and V. In mixed venous blood, P_{O_2} decreased, P_{CO_2} and $/H^+/$ increased. The change in $P_{\bar{v}CO_2}$ during the hypovolemic phase (between periods III and V) was not significant, but the continued increase in $/H^+/$ (between periods III and V) was significant ($P < 0.01$). These changes resulted in a considerable increase in arteriovenous P_{CO_2} and $/H^+/$ gradients.

Effects of Reinfusion. Systemic arterial pressure remained lower ($P < 0.01$) than during the resting period, and cardiac output was restored to a level not significantly different from the resting value. Arterial blood gases and $/H^+/$ were not significantly different from the hypovolemic values. $P_{\bar{v}O_2}$ increased ($P < 0.01$) but remained lower ($P < 0.05$) than during the control period. $/H^+/_{\bar{v}}$ remained elevated, and in both postreinfusion periods (VI–VII) it was higher ($P < 0.02$) than the resting value. $P_{\bar{v}CO_2}$ decreased.

All dogs relapsed into shock and died within 4.5 (±1.5) hours after reinfusion of the shed blood.

GROUP B: HYPERVENTILATED DOGS

Effects of Assisted Ventilation (Period II). Cardiac output and blood pressure were not significantly affected, plasma lactic acid in-

TABLE 2. Effects of Hemorrhage on Arterial and Mixed Venous O_2 and CO_2 Tensions and $/H^+/$ in Intact (A) and Hyperventilated (B) Dogs and in Dogs Subjected to Combined ($\alpha + \beta$) Adrenergic Receptor Blockade (C)

	Group	P_{AO_2} (torr)	$P\bar{v}_{O_2}$ (torr)	P_{ACO_2} (torr)	$P\bar{v}_{CO_2}$ (torr)	$/H^+/_A$ (mμEq/l)	$/H^+/_{\bar{v}}$ (mμEq/l)
Period I, control	A	86(10)	53(4)	42(5)	46(5)	46(5)	47(5)
	B	87(8)	51(6)	40(9)	44(8)	43(4)	45(4)
	C	82(13)	50(9)	42(8)	46(7)	42(4)	44(4)
Period II, control on assisted ventilation	B	103(9)	43(6)	15(7)	21(5)	28(5)	30(5)
Period III, 40 min after commencement of bleeding	A	91(6)	28(8)	36(5)	60(15)	50(4)	60(6)
	B	108(2)	22(6)	15(3)	33(11)	39(7)	48(9)
	C	81(11)	27(5)	40(6)	54(6)	47(5)	53(5)
Period IV, 90 min after commencement of bleeding	A	85(6)	23(4)	33(4)	69(4)	56(5)	71(6)
	B	109(5)	22(5)	16(7)	51(13)	54(14)	75(14)
	C	84(4)	24(4)	36(7)	54(6)	47(6)	54(7)
Period V, 170 min after commencement of bleeding	A	87(9)	24(4)	36(5)	74(11)	60(6)	74(11)
	B	104(7)	24(8)	16(7)	52(14)	54(16)	73(28)
	C	87(9)	22(3)	32(10)	55(11)	45(7)	55(9)
Period VI, 30 min postreinfusion	A	83(20)	43(9)	44(11)	64(25)	67(14)	72(19)
	B	104(3)	44(7)	19(5)	30(10)	54(22)	59(26)
	C	84(9)	40(3)	33(10)	42(7)	46(8)	49(8)
Period VII, 90 min postreinfusion	A	85(22)	40(5)	38(19)	53(15)	56(14)	62(14)
	B	93(14)	45(9)	35(7)	50(10)	66(22)	71(25)
	C	79(8)	40(6)	36(6)	45(8)	46(5)	49(6)

creased ($P < 0.02$), P_{AO_2} increased ($P < 0.02$), and both mixed venous and arterial P_{CO_2} and $/H^+/$ values decreased ($P < 0.01$). The decrease in $P\bar{v}_{O_2}$ was not significant.

Effects of Hemorrhage (Periods III–V). Cardiac output fell to the same extent as in the previous group, but mean blood pressures in periods IV and V were lower ($P < 0.05$) than the corresponding values in the control group. In periods III and IV plasma lactic acid concentrations were higher ($P < 0.02$) than during the corresponding periods in the controls, but in the last hypovolemic period (Period V) this difference was no longer significant. P_{AO_2} remained constant and $P\bar{v}_{O_2}$ decreased as in the controls. P_{ACO_2} remained constant and $P\bar{v}_{CO_2}$ increased progressively but remained lower than in the controls. $/H^+/_A$ increased, and in periods IV and V the values were no longer significantly different from the corresponding values in the controls; $/H^+/_{\bar{v}}$ increased, and in periods IV and V the values were virtually identical to the corresponding values in the control group.

Volumes of blood shed by these dogs were comparable to values for the controls.

Effects of Reinfusion. After reinfusion of the shed blood, but while ventilation still was assisted (period VI) cardiac output increased, but it remained lower ($P < 0.01$) than during period II; blood pressure was not significantly different from that in period II, and there were no significant changes in arterial blood gases and $/H^+/$. In the mixed venous blood, P_{O_2} increased and P_{CO_2} and $/H^+/$ decreased, but the latter change was not significant.

After spontaneous breathing had been restored (period VII), blood pressure remained lower ($P < 0.01$) than in period II. Arterial and mixed venous P_{CO_2} and $/H^+/$ values increased ($P < 0.01$), and the latter were higher ($P < 0.05$) than in period I.

All dogs relapsed into shock and died within 6.3 (±0.7) hours after reinfusion of the shed blood.

Group C: Treated Dogs

Effects of Blockade (Period I). There were no significant differences from the control values of the two previous groups.

Effects of Hemorrhage. Changes in cardiac output were not significantly different from the corresponding values in the two previous groups; blood pressure was similar to that of group B and lower ($P < 0.02$) than that in the control group. Changes in arterial and mixed venous P_{O_2} were similar to those in group A, but changes in arterial and mixed venous P_{CO_2} failed to attain statistical significance. There was no significant change in $/H^+/_A$, and the increases in $/H^+/_{\bar{v}}$ ($P < 0.01$) in all three hypovolemic periods were less ($P < 0.01$) than those in the previous two groups. There was no significant change in plasma lactic acid.

Blood loss in these dogs was comparable to blood losses in the previous two groups.

Effects of Reinfusion. Cardiac output increased but remained lower ($P < 0.01$) than during the control period. Blood pressure was first restored to near-control level but then fell, and in period VII it was lower ($P < 0.05$) than during the control period. Blood gases and acid–base composition were not significantly affected.

Next morning, 18 hours after reinfusion of the shed blood, all dogs were alive.

Discussion

The severe venous hypercapnia in shocked dogs with normal or reduced P_{ACO_2} values suggests that respiratory compensation, unless excessive, was limited to the alveolar–arterial compartment and, contrary to previous claims,[14] would not effectively reduce tissue P_{CO_2}. With an excessive increase in ventilation produced by mechanical assistance, both arterial and mixed venous P_{CO_2} values fell, yet the shock-induced rise in the arteriovenous P_{CO_2} gradient remained unaffected and extracellular acidity was aggravated by the additional stimulation of lactic acid release, a well-known sequel of arterial hypocapnia.[15] In our dogs P_{CO_2} was in the vicinity of the level which in respiratory failure is considered the limit of consciousness,[16] and this may partly account for the fact that shocked animals require so little anesthesia. We are prompted to conclude that, contrary to accepted views, tissue acidosis in shock should not be classified as purely metabolic: its hypercapnic component remains concealed only when arterial blood is used for analysis. Hidden tissue hypercapnia in shock offers a further explanation for the therapeutic inefficiency of sodium bicarbonate infusion,[17] and is likely to contribute to the postreinfusion increases in $/H^+/_A$ and P_{ACO_2}.[11]

The slope of the total-body CO_2 dissociation curve increases with time, and for experiments lasting as long as two hours is approximately 1.7 ml/kg/torr.[4] In the absence of data for longer periods, we used this value for our three-hour experimental period, and it is likely, therefore, that our calculations represent an underestimate. Assuming that arterial and mixed venous P_{CO_2} represent alveolar and tissue P_{CO_2} levels, the total volume of CO_2 retained in both spontaneously-breathing and hyperventilated bled dogs amounted to 1.2 l, or 5 per cent of resting CO_2 output. This probably would have escaped attention even if expired air had been collected continuously.

In intact dogs, the arteriovenous P_{CO_2} gradient was influenced by the duration of hypotension and by blood flow. Cardiac output remained stable during hypovolemia, yet the arteriovenous P_{CO_2} gradient increased in the first 80–100 min and remained constant afterwards. More prolonged observations were obviated by the spontaneous uptake of blood from the reservoir, which usually commenced at 150–170 min. Using only values obtained after 90 min of hypovolemia, the relationship of blood flow and the arteriovenous P_{CO_2} gradient is shown in figure 1, and can be expressed by the equation:

$$Y = -14.95X + 53.2$$
$$r = -0.7364$$

where Y = arteriovenous P_{CO_2} gradient, torr; X = cardiac output in l/min/m²BSA; r = regression coefficient.

We suggest that the absence of an arteriovenous P_{CO_2} gradient in Zahn's and Weil's patients[7] was probably the result of an absence of profound reduction in blood flow.

Venous desaturation is viewed as an indicator of the severity of shock. Comparing O_2 extraction ratios and arteriovenous P_{CO_2} gradients we found (fig. 2) that the gradient

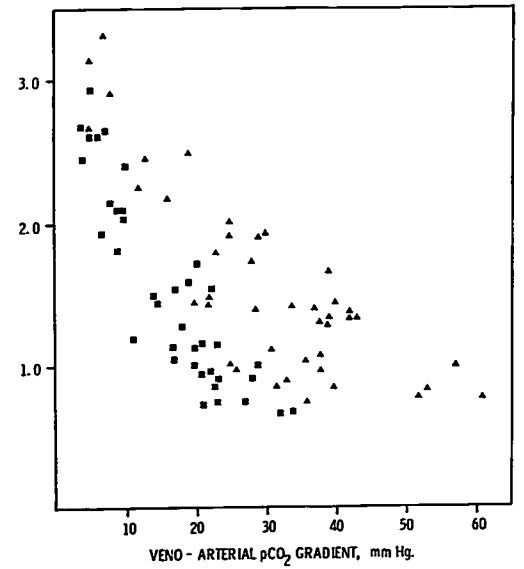

FIG. 1. Relationship of blood flow and arteriovenous P_{CO_2} gradient in nonmedicated shocked dogs (solid triangles) and in shocked dogs premedicated with phenoxybenzamine and propranolol (solid squares). Values included in this diagram were obtained no sooner than 90 min after the start of bleeding. Regression equations are shown in the text.

continued to rise even after the O_2 extraction ratio reached its natural limit. It appears that P_{CO_2} may be a more useful index of the extent and duration of reduced tissue perfusion than P_{CO_2}.

In the treated animals hemorrhage-induced venous hypercapnia was reduced: for comparable values of cardiac output the arteriovenous P_{CO_2} gradient was significantly less than in nonmedicated animals (fig. 1); this relationship can be expressed by the equation:

$$Y = -10.96X + 33.4$$
$$r = -0.8910$$

This was parallel to, but distinct from, the regression line obtained for nonmedicated animals. Using the same calculation as before, treated animals stored 360 ml of CO_2, representing only 1.9 per cent of resting CO_2 production, or less than half of that retained by nonmedicated animals. Since the hemodynamic states of the two groups of dogs were virtually identical, this could not be accounted for by improved tissue perfusion, but rather must have been caused by blockade-induced suppression of the calorigenic effect of endogenous catecholamines, resulting in reduced CO_2 production.

Owing to venous hypercapnia, $/H^+/_{\bar{v}}$ in shocked dogs was 10–15 mμEq/l higher than $/H^+/_A$, and since peripheral venous lactate levels tended to exceed those of the mixed venous blood, acidemia in the peripheral veins probably was even more pronounced. Brown *et al.*[9] found in hemorrhagic shock that extracellular $/H^+/$ is closely related to intracellular $/H^+/$ in muscle. Using their regression equation and substituting $H^+/_{\bar{v}}$ for extracellular $/H^+/$, the calculated intracellular $/H^+/$ in our dogs increased to 165 mμEq/l. Measured total-body intracellular $/H^+/$ in bled dogs breathing 3 per cent CO_2 ranges from 140 to 187 mμEq/l.[14]

In these experiments lactic acid levels in plasma were poorly related to $P_{\bar{v}O_2}$, and the relationship between the latter and $/H^+/_{\bar{v}}$ (figure 3) probably was determined by P_{CO_2}.

Combined adrenergic receptor blockade sup-

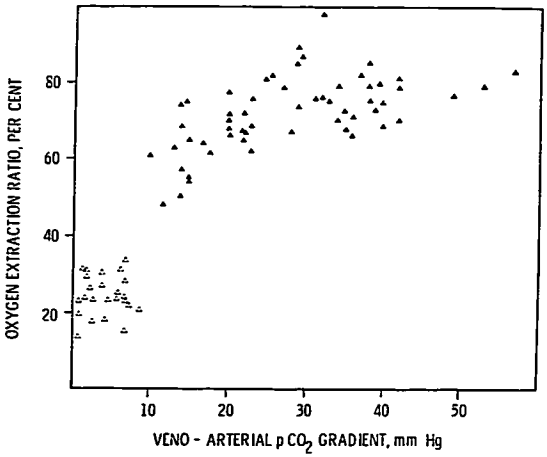

FIG. 2. Relationship of the oxygen extraction ratio and arteriovenous P_{CO_2} gradient in normovolemic (open triangles) and hypovolemic (solid triangles) dogs.

pressed both lactic acid release and CO_2 production, resulting in a lesser increase in $/H^+/_{\mp}$: for the same values of $P_{\bar{v}O_2}$, $/H^+/_{\mp}$ remained lower in treated than in nonmedicated dogs (fig. 3), and this difference was significant. Since combined adrenergic receptor blockade also prolongs survival, the possible relationship between extracellular acid-base composition and tolerance to hemorrhage requires further analysis.

Severity and outcome in clinical and experimental shock are poorly related to arterial

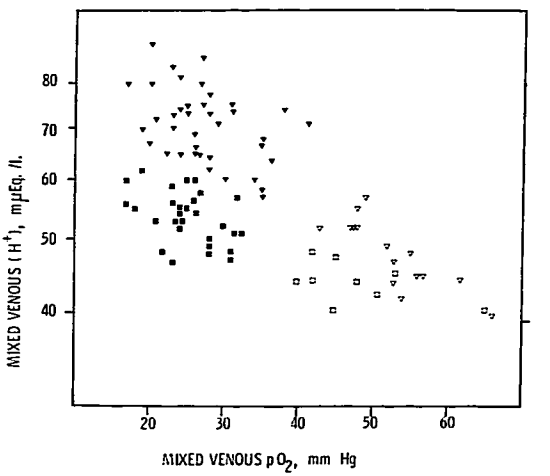

FIG. 3. Relationship of mixed venous P_{O_2} and $/H^+/$ in normovolemic (open figures) and hypovolemic (solid figures) dogs. Nonmedicated dogs are represented by triangles; animals subjected to $\alpha + \beta$ adrenergic receptor blockade, by squares.

acid–base composition,[18, 19] and the dissociation between arterial and extracellular $/H^+/$, as shown here, offers a valid excuse for the lack of such correlation. $/H^+/_{\bar{v}}$ in all our bled animals fatally shocked exceeded 65 mμEq/l, while remaining below 60 mμEq/l in all those which remained alive during the period of observation. On the other hand, the administration of tris buffer, known to correct intracellular acidosis, fails to improve survival rate in hemorrhagic shock,[20, 21] and extracellular acidosis of comparable severity (although of shorter duration) may occur in exercise.[22] Consequently, our experiments should not be interpreted as suggesting that extracellular acidosis is causally related to irreversibility, but $/H^+/_{\bar{v}}$ does appear to have a closer relationship to prognosis than $/H^+/_A$.

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Drugs

PENTAZOCINE ANALGESIA In a double-blind assay, *d*-pentazocine was compared with *l*-pentazocine given principally for postoperative pain. It appears that analgesia resides principally in the *l*-isomer. (*Forrest, W. H., Jr., and others: Analgesic and Other Effects of the d- and l-Isomers of Pentazocine, Clin. Pharmacol. Ther. 10: 468 (July) 1969.*)