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# METABOLIC ACIDOSIS AND SEVERE HYPOTENSION: INFLUENCE ON SURVIVAL TIME AND SHOCK PERIOD DURING HEMORRHAGE IN THE CAT

G.A. DEHGHANI, Ph.D. AND H. NAJAFIPOUR, Ph.D.

*From the Department of Physiology, Shiraz University of Medical Sciences, Shiraz, Islamic Republic of Iran.*

## ABSTRACT

Metabolic acidosis and severe hypotension are the main causes of irreversibility during hemorrhagic shock. The influence of these two factors on durations of shock period and survival time were studied in four groups of anesthetized cats. In group I the animals were made hypotensive by reducing mean arterial blood pressure (Pa) to 45 mmHg with concurrent metabolic acidosis. In group II the same level of hypotension was produced, along with an intravenous infusion of 12% sodium bicarbonate solution (0.25 ml/kg/min.); thus metabolic acidosis was prevented and arterial blood pH (pHa) was kept within its normal range. In group III the Pa was kept at 50 mmHg in the presence of metabolic acidosis, and in group IV, the Pa was kept at 50 mmHg (the same as group III) but acidosis was prevented. Durations of shock period and survival times of all groups were compared. The results of this study show that 1) preventing metabolic acidosis increased survival time by 400%, 2) keeping the Pa at 50 mmHg increased survival time by 800 percent, and 3) prevention of metabolic acidosis at a Pa of 50 mmHg still augmented survival time by more than 250 percent. We therefore conclude that control of pHa and prevention of severe hypotension may increase survival rates in patients suffering from hemorrhage.

**Keywords:** Hemorrhage; hypotension; metabolic acidosis; survival time

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## INTRODUCTION

The pathophysiology of shock has been the subject of vast research. Extensive research has shown that the production of peptide agents named myocardial depressant factors (MDFs) act as positive feedback loops culminating in irreversibility during prolonged shock periods.[1,7] However, few researchers have attempted to study ways to prevent or reduce the production of these deadly agents during hemorrhagic shock.[1,7,9,11,14,17]

The purpose of this study was to find out if prevention of metabolic acidosis can increase the survival rate of animals whose life is threatened by severe hypotension. Experiments were also carried out to test the hypothesis that survival time increasesextensively if arterial blood pressure of the animal in shock does not get too close to the critical closing pressure (PCC).

## MATERIALS AND METHODS

Experiments were performed on 24 cats weighing 2.4-4.5 kg. The animals were anesthetized by intraperitoneal injections of 30 mg/kg sodium pentobarbital. The left femoral artery and vein were cannulated in order to measure arterial blood pressure, obtain arterial blood samples and



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**Table I. Arterial blood pH changes during experiments***

| | Period of hemorrhage (min.) | | Period of shock (min.) | | Survival time (min.) | |
|---|---|---|---|---|---|---|
| | CNT | 20 | 40 | 90 | 15 | 90 |
| Group I (N= 6) | 7.40 ±0.02 | 7.46 ±0.03 | 7.10** ±0.03 | 6.95** ±0.06 | 7.10** ±0.05 | 7.12** ±0.04 |
| Group II (N= 6) | 7.40 ±0.03 | 7.52 ±0.05 | 7.42 ±0.03 | 7.40 ±0.02 | 7.41 ±0.03 | 7.45 ±0.04 |
| Group III (N= 6) | 7.42 ±0.03 | 7.46 ±0.03 | 7.12** ±0.04 | 7.10** ±0.05 | 7.20** ±0.08 | 7.25** ±0.04 |
| Group IV (N= 6) | 7.40 ±0.02 | 7.45 ±0.03 | 7.41 ±0.02 | 7.38 ±0.04 | 7.30 ±0.05 | 7.40 ±0.04 |

* = Values are expressed in mean ±SE

** = Values are significant relative to control at P<0.05

infuse fluid and drugs into the circulation as needed. The right femoral artery was cannulated and connected to a graduated reservoir via coiled silastic tubing. Tracheotomy was done to bring the animal's breathing under control. A gas mixture of 35% $O_2$, 5% $CO_2$ and 60% $N_2$ was given to the animals during surgery and during the experiment to reduce the possibility of arterial hypoxemia and its interaction with severe hypotension. At the end of surgery the animal was maintained at rest for at least three hours in order to reduce the effects of trauma as much as possible. Just at the start of the experiment the animal was heparinized by an intravenous infusion of 1500 U/kg of heparin, allowing us to bleed the animal into the reservoir without worrying about clotting.

The bleeding instrument was made of a graduated plastic container that could be placed at selected heights above the heart level. A two meter coiled silastic tube was placed in a Ban-Marie with a temperature of 37±1°C. One end of this tube was connected to a reservoir and the other end to the right femoral arterial cannula. The rectal temperature was recorded by a thermistor and kept at 37±1°C by warming the animal with an electric lamp. Left femoral arterial and venous catheters were connected to Statham pressure transducers connected to a Grass polygraph. A continuous recording of arterial and venous blood pressures was made during the periods of control, hemorrhagic shock, and reinfusion of shed blood and terminated when the Pa stabilized at 60 mmHg. From arterial pressure traces pulse and respiratory rates were recorded.

Severe hypotension was provoked by keeping the plastic container 61 cm or 68 cm above the heart level and opening the right arterial cannula. The bleeding procedure continued until a fixed Pa (45 mmHg in groups I and III and 50 mmHg in groups II and IV) was obtained. This cannula was left open to reduce the reflex compensatory effects on Pa. The animal was left in this condition until about 40% of the collected blood in the container had returned into the circulation. The shock period was terminated at this time by gradually raising the reservoir height and reinfusing the rest of the shed blood into the circulation. This procedure was carried out slowly during a 15 minute period in order to prevent the central venous pressure from rising more than 2.5 mmHg above normal. Survival time was considered to begin when all the extruded blood had returned into the circulation, and end when the Pa reached 60 mmHg. This final pressure was chosen because it has been shown that after reinfusion of shed blood, survival rates approach zero when the Pa approaches 60 mmHg.[11,13,14]

**Experimental Protocol**

The animals were divided into four groups:

**Group I:**

The animal was bled until its Pa reached 45 mmHg without controlling the pHa. In this group, a metabolic acidosis with a pHa of 7.05±0.02 was always present. A slow intravenous infusion of normal saline (0.25 ml/min) was administered to be able to compare the obtained data with that of other groups.

**Group II:**

Bleeding was performed as in group I but a solution of 12% hypertonic sodium bicarbonate was infused at a rate of 0.25 ml/min (up to a total of 2.5-3.0 ml/kg) in order to increase the buffering capacity of the blood. This infusion was continued so as to prevent the induction of metabolic acidosis during hemorrhagic shock. This procedure allowed us to keep the pHa within its normal range of 7.4±0.015 during the experiment.



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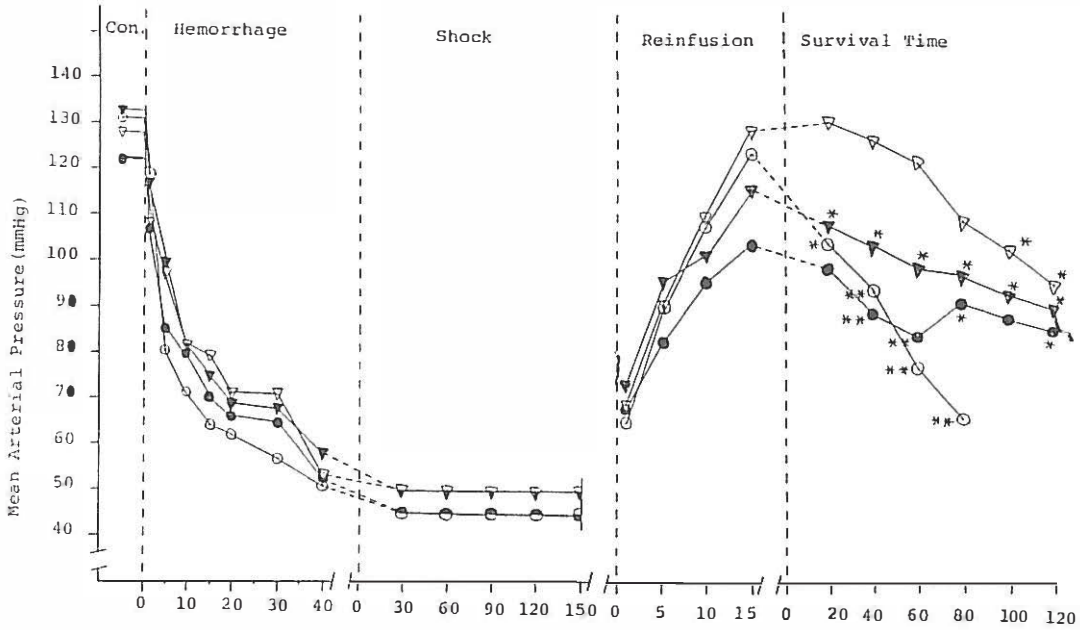



**Fig. 1.** Mean arterial blood pressure during control (CNT), hemorrhage, shock period, reinfusion of blood, and survival time, * = significantly different from control.

**Group III:**

The reservoir height was kept at 68 mmHg to keep the Pa at 50 mmHg (5 mmHg above PCC), but other conditions were the same as in group I. In this group the pHa was 7.04±0.03

**Group IV:**

All conditions were the same as in group III, except that metabolic acidosis was prevented by methods similar to group II. In this group the pHa was 7.40±0.02.

**Statistical analysis**

Student's t-test was used to analyze the differences among the values of pHa, shock period and survival time of the four groups. The levels of significance were considered when P-values were less than 0.05 ($P<0.05$).

## RESULTS

**Mean arterial blood pressure (Pa)**

Variations of Pa were recorded continuously during control, hemorrhage, transfusion of blood and survival time. As shown in Fig. 1, there was a steep decline in Pa in groups I and II to about 45 mmHg and to 50 mmHg in groups III and IV during bleeding. These pressures were maintained at that level until 40% of the shed blood had returned to the circulation. Reinfusion of the shed blood caused a great increase in Pa to about 124±13, 104±5, 129±5, and 116±13 mmHg in groups I through IV respectively. Despite reinfusion of all of the shed blood into the circulation, the animals of all groups could not maintain their Pa at normal levels for a prolonged period. This decrease was much more pronounced in groups I and III whose pHa was not controlled.

**Heart rate**

Alterations in the heart rate of the four groups are presented in Fig. 2. The control heart rates, however, were always higher than what is reported in normal conscious cats but there were not significant differences among the four groups.

**Arterial blood pH**

During the first 20 minutes of bleeding, the pHa increased in all animals. In groups I and III, the pHa started a gradual decrease, reaching bottom values of 6.95±0.06 and 7.00±0.05, respectively. The reduction of pHa was prevented by a slow infusion of sodium bicarbonate in groups II and IV.

**Shock period**

Fig. 3 shows the durations of shock periods and survival time in all four groups. The mean duration of shock was much longer in groups II and IV with controlled pHa in comparison to groups I and III in which metabolic acidosis was present. This shows that prevention of metabolic acidosis lowers the tolerance of the animal in overcoming the effects of circulatory shock.



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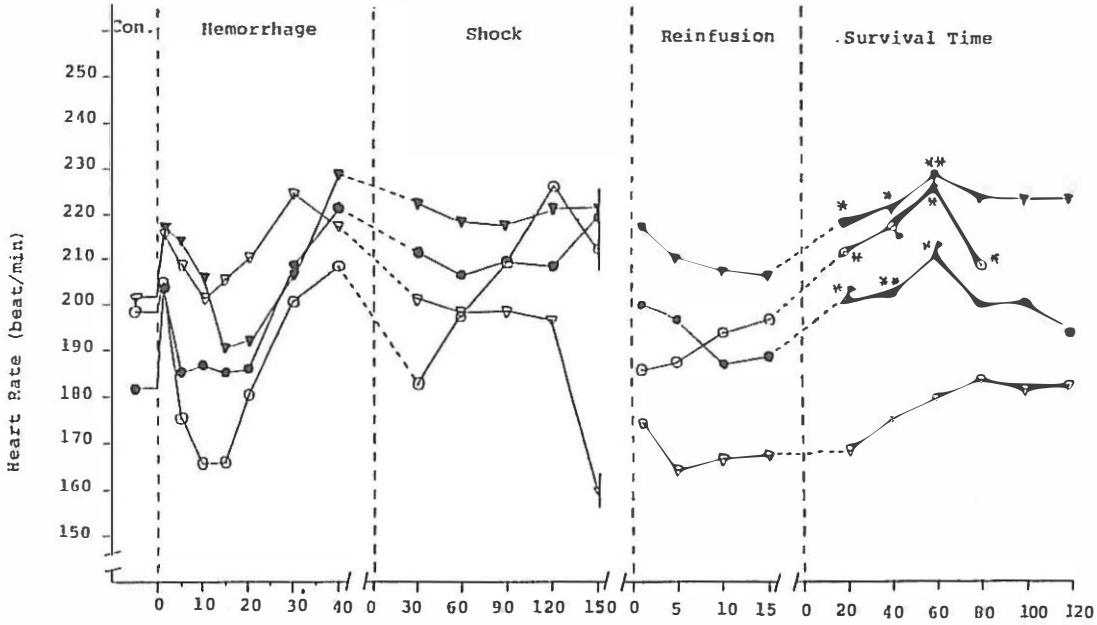



**Fig. 2.** Heart rate during control (CNT), hemorrhage, shock period, reinfusion of blood, and survival time.

### Survival time

Fig. 3 also compares survival times in group I with severe metabolic acidosis and in group II with a normal pHa. The mean duration of survival of group II animals was about 340 minutes; that is, almost four times that of animals with metabolic acidosis. Elevating the Pa to only 5 mmHg above PCC in group III animals caused an increase in survival time to 801±300 min (10 times more than that of group I). By both preventing metabolic acidosis and slightly raising the Pa, survival time was further prolonged to 1539±310 minutes (20 times longer than that of group I).

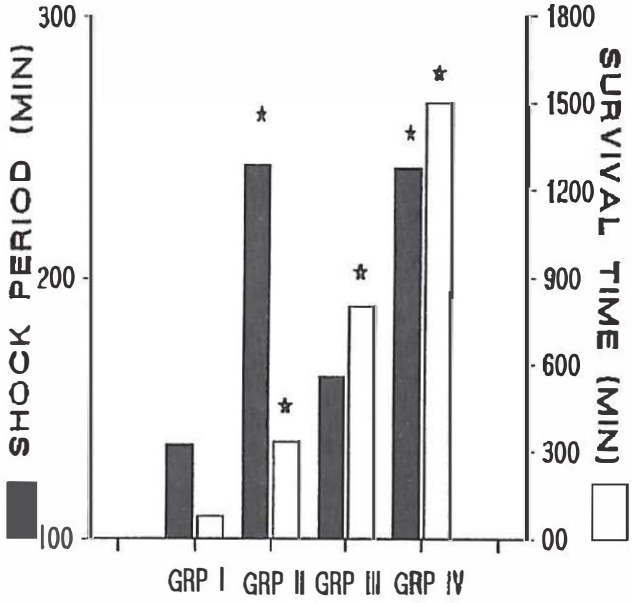



**Fig. 3.** Shock period and survival time relative to group.

## DISCUSSION

Severe hypotension is a life-threatening problem during accidents, and hemorrhage is the main cause of hypovolemia and hypotension. The primary defect that characterizes severe hypotension is acute perfusion impairment of all organs in which metabolism is critically curtailed by reduced delivery of oxygen to tissues. Perfusion failure is mainly identified by the development of lactic acidosis. Investigators have shown that the main cause of death that occurs in dogs with this condition is the production of many poisonous agents (including MDFs) and development of acidosis.[8,11,13] Although the development of lactic acidosis is an indicator of irreversibility in animals in shock,[12] it is not known whether the correction of acidosis will decrease mortality rates in severe hypotension or not.

There are reports suggesting that treatment of hemorrhagic rats with 100% $O_2$ attenuates the increased plasma activity of lysosomal hydrolase enzymes, and these animals exhibit significantly longer survival times.[3] From these observations, Bitterman and his group concluded that giving pure $O_2$ to those who suffer from hemorrhagic shock exerts important beneficial effects and may be a useful method for treating these patients.[3] In this study, we therefore eliminated the interaction of arterial hypoxemia by keeping the $PaO_2$ well above 150 mmHg.



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**Hemorrhage and the respiratory system**

There was a significant increase in respiratory rate upon inducing severe hypotension. Reports in the literature reveal that arterial hypotension stimulates carotid chemoreceptors,[2] therefore improving alveolar ventilation.[6,15] The outcome of this effect is the respiratory alkalosis which was observed at the beginning of the bleeding period in all groups.

**Hemorrhage and survival time**

Survival time isa good index for indicating how long the cardiovascular system can tolerate the deteriorating effects of severe hypotension. It has been shown that prolongation of hemorrhagic shock, especially when the Pa reaches 40 mmHg or less, damages the integrity of the CVS so quickly that the patient goes into irreversible shock and dies within hours.[16] It is also reported that during severe hypotension a huge amount of lactic acid (10 times normal) is produced which enters the circulation.[15] Reduction of $O_2$ delivery due to metabolic acidosis also releases lysosomal enzymes from poorly perfused organs.[9] The release of these enzymes produces MDFs which have strong negative inotropic effects on the heart.[11]

We found out that lowering the Pa of anesthetized cats to 45 mmHg reduced survival time to 77±10 minutes. It is worth mentioning that at this point which is called the "critical closing pressure", most arteriolar beds are closed and harbor no blood flow.[17] As shown in Fig. 5, keeping the Pa only 5 mmHg above the PCC during the shock period increased the survival time to 330±35 minutes. Therefore, we believe that quick termination of severe hypotension (until the Pa reaches the PCC level) has beneficial effects in increasing the tolerance of patients in shock.

As presented in Table I, we found that severe metabolic acidosis always accompanies severe hypotension. Comparison of the pHaof groups I and III is indicative of the level of irreversibility. Some investigators have revealed that high concentrations of H ions have strong deteriorating effects on the CVS.[1,3,5] Prevention of metabolic acidosis by slow intravenous infusion of 12% sodium bicarbonate (0.25-0.3 ml/kg) was an interesting way to fight severe acidosis without being worried about the interaction of volume expansion on CVS responses in severe hypotension.[21]

Comparison of the results of survival time (Fig. 3) between conditions of a Pa of 45 mmHg and acidosis with that of a Pa of 50 mmHg and a normal pHa revealed staggering results that have never been reported in the literature. Preventing metabolic acidosis in group II magnified the survival time by a factor of four. Retaining the Pa of bleeding animals only 5 mmHg above the PCC increased survival time more than 10 times. Preventing metabolic acidosis in these conditions raised the survival time even further to about 1539±310 minutes—22 times higher than what was observed in group I.

Moreover, it is also worth noting that heart rates remained unchanged in all groups even when animals passed the final stages of their survival time (Fig. 2). This manifests that the activity of pacemaker cells in the sino-atrial node and the ventricular conductive system were not greatly curtailed by low perfusion pressure and severe metabolic acidosis. Hence observation of pulse rates or the ECG as the only vital signs in hemorrhagic patients might cause a misjudgement of the deteriorating conditions of the patient.

In conclusion, the results of this observation revealed that control of metabolic acidosis during severe hypotension increases the survival period by about five times when the arterial pressure is at the PCC level during shock. Keeping the arterial pressure 5 mmHg above the critical closing pressure increases the survival period by 10 times. Preventing metabolic acidosis at this stage increases the survival period hy more than 20 times. Therefore, prevention of metabolic acidosis and severe hypotension may increasethe survival rate of pateints suffering from hemorrhage enormously.

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