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Effects of Inspiratory Oxygen Concentration and Ventilation Method on a Model of Hemorrhagic Shock in Rats

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Abstract: *The effect of inspiratory oxygen concentration and the ventilation method on hemorrhagic shock was investigated. Twenty-eight rats were divided into four groups: mechanical ventilation with pure oxygen (M100); mechanical ventilation with air (M21); spontaneous respiration with pure oxygen (S100); and spontaneous respiration with air (S21). Under intravenous pentobarbital anesthesia, hemorrhagic shock (HS) was induced by withdrawal of blood from the femoral artery. Mean arterial blood pressure (MAP) was maintained at 40–50 mmHg for 2 h. After HS, the blood remaining in the reservoir was reinfused. Then survival rate and MAP were monitored for 2 h. Blood samples were withdrawn and vascular reactivity to norepinephrine (NE; 3.0 μg/kg) was tested before and after HS. Results were shown by changes in MAP in response to NE. During HS, the survival rate of the S21 group was lower than that of the M100 and S100 groups ($p<.05$). Before HS, MAPs of M100 and S100 groups were significantly higher than those of M21 and S21 groups ($p<.05$). In the M100 and M21 groups, MAPs at 2 h after reinfusion were significantly lower than the baseline value ($p<.05$). Before HS, reactivity to NE of the M21 group was significantly higher than that of the other groups ($p<.05$). In the M21 group, reactivity to NE after HS was significantly lower than it was before HS ($p<.05$). Inspiratory oxygen concentration and the ventilation method affect the survival rate and vascular reactivity of the rat hemorrhagic shock model. Selection of the inspiratory oxygen concentration and the ventilation method should be made according to the purpose of the individual experiment.*

Key words: *hemorrhagic shock, oxygen concentration, rat, ventilation method*

Introduction

Various experiments concerning hemorrhagic shock (HS) have been performed using rats. Because many factors such as inspiratory oxygen concentration, mechanical ventilation methods or spontaneous breathing condition, method of anesthesia, duration of HS, and preparation method of HS may affect the experimental results, these models of HS have not been unified.

Increasing the inspiratory oxygen concentration causes a rise in the mean arterial pressure (MAP) and in the peripheral vascular resistance due to arterial vaso-

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constriction [1, 2]. Some authors have reported beneficial effects [3, 4], while others [5] could not find any advantage of high oxygen concentration in HS. However, arterial vasoconstriction may damage the peripheral circulation and affect experimental results.

Also there must be a difference in the intrathoracic pressure between spontaneous respiration and the mechanical ventilation methods, which affects the venous return and circulatory dynamics [6]. Hyperventilation to compensate for metabolic acidosis, which is caused by HS, is observed in the rat undergoing spontaneous respiration. On the other hand, it is necessary to examine the ventilatory condition by analyzing arterial blood gases according to the experimental protocol in the mechanically ventilated rat. When considering these factors affecting the state of HS, it becomes clear that we should select the conditions for the rats in accordance with the purpose of the individual experiment.

The purpose of this study was to evaluate the effect of inspiratory oxygen concentration and the method of ventilation on the mortality and vascular reactivity to a vasoconstrictor agent in a constant blood pressure HS model using rats.

Materials and Methods

The Animal Care Committee of Hamamatsu University School of Medicine approved this study (No. H-13-28-06), and the experimental protocol followed the Guide for the Care and Use of Laboratory Animals of the Hamamatsu University School of Medicine. This study was performed at the laboratory of the Department of Anesthesiology and Intensive Care, Hamamatsu University School of Medicine.

Male Sprague-Dawley rats (310 to 400 g SLC, Inc. Japan) were allowed free access to food and water until the experiment began. During the experiment all rats were anesthetized with pentobarbital sodium (50 mg/kg i.p.). Their body temperature was measured by a rectal thermistor probe and maintained at 37°C using a heating pad. A tracheotomy was surgically performed, and a cannula was placed in the trachea for tracheotomy breathing or artificial ventilation. The 28 rats were divided into four groups. Spontaneous respiration group (S21 group) animals were allowed to breathe room air (21% O_2) spontaneously. Spontaneous respiration with pure oxygen group (S100 group) animals were allowed to breathe pure oxygen (100% O_2) spontaneously. Controlled ventilation group with air (M21 group) animals were ventilated mechanically with room air (21% O_2). Controlled ventilation group with pure oxygen (M100 group) animals were ventilated mechanically with pure oxygen (100% O_2). A ventilator (RODENT VENTILATOR model 683, Harvard Apparatus, South Natick, MA) was used for mechanical ventilation. The tidal volume was maintained at 2 ml and the respiratory rate was at 80 cycles/min.

The left femoral vein was cannulated with a PE50 catheter for the infusion of drugs and fluids. The left femoral artery was also cannulated with a PE50 catheter which was connected to a transducer (VAMP plus™, Baxter, Irvine, CA) for measurements of MAP. Saline (1 ml/h) was infused continuously to prevent occlusion of the catheter. MAP and temperature were continuously measured (HP 78534C, Hewlett-Packard, Avondale, PA). MAP was recorded continuously by a PC based data acquisition system (T3600, Toshiba, Tokyo, Japan). Blood loss was quantified with a gauze sponge during the surgical procedure. Saline (1 ml/h) with sodium pentobarbital (20 mg/kg/h i.v.) infusion was started in all groups to maintain adequate anesthesia during the experiment. Pancronium bromide (Sankyo, Tokyo, Japan) (0.1 mg/kg/h i.v.) was added to the M21 group and M100 group to reduce spontaneous ventilation. Following the end of the surgical procedure, heparin sodium (100 U) was administered intravenously.

After a stabilization period (15 min), 0.4 ml of arterial blood sample (HS-0) was obtained for arterial blood gas analysis (ABG) and plasma nitrite (NO_2^-) and nitrate (NO_3^-) measurements. The levels of NOx (NO_2^- plus NO_3^-) were measured by means of high performance liquid chromatography using the Griess reaction after the reduction of NO_3^- to NO_2^- (ENO-20™, Eicom, Kyoto, Japan) [7] to evaluate the NO production related to the vascular tone. Fifteen minutes after the blood sampling, norepinephrine (Sankyo, Tokyo, Japan) 3.0 μg/kg was injected in order to evaluate the vascular reactivity (NE-1). Fifteen minutes later, blood was withdrawn via the catheter in the femoral artery by a sterilized syringe to induce HS. MAP was maintained between 40 to 50 mmHg for 120 min. When MAP was more than 50 mmHg, 0.5 ml of blood was withdrawn, and when MAP was less than 40 mmHg,

0.5 ml of blood was infused. Sixty minutes after the induction of HS, an arterial blood sample was obtained for ABG (HS-60).

In the M21 and M100 groups, the tidal volume was increased to 3 ml from 2 ml and the respiratory rate was increased to 100 cycles/min from 80 cycles/min in order to decrease $PaCO_2$ for treatment of acidosis. Another arterial blood sample was obtained for ABG and NOx measurement at 115 min after induction of HS (HS-120). During HS, the maximum value of shed blood volume was recorded. After 120 min of HS, the withdrawn blood was reinfused over 5 min. Arterial blood samples were obtained for ABG at 2 min after reinfusion (RE-2) and 15 min after reinfusion for ABG and NOx measurement (RE-15). The second NE test (NE-2) was performed 30 min after the reinfusion. Following NE-2, we observed the animal for the next 90 min. An arterial blood sample was obtained for ABG and NOx measurement at 120 min after reinfusion (RE-120). The third NE test (NE-3) was performed after the blood sampling. The results of the NE test are shown by percent changes in MAP in response to NE. Animals that survived until the end of the experiment were sacrificed by an overdose of sodium pentobarbital.

All values in the text and figures are given as the mean ± standard error of the mean (SEM). The survival rate was analyzed using Fisher's exact test. Comparisons were made using an analysis of variance (ANOVA) with a post-hoc Tukey-Kramer test. $p<.05$ was the criterion for statistical significance.

Results

Survival Rate

The survival rates of the four groups are illustrated in Table 1. During HS of 120 min, the S21 group had the lowest survival rate among the four groups. In this group, the major symptom was respiratory arrest, after which the rats died during HS. Though the survival rate in the S21 group did not decrease after recovery from HS, the survival rate in the S100 and M100 groups decreased even after recovery from HS.

Maximum Shed Blood Volume

The average shed blood volume during HS for the four groups is shown in Table 2. The amount of shed blood in the M100 and S100 groups had a tendency to be large ($p=.06$).

Hemodynamic Variables

The changes in MAP of the four groups are shown in Table 3. Before HS (HS-0), the MAPs of the M100 and S100 groups were significantly higher than those of the M21 and S21 groups ($p<.05$). In the M100 and M21 groups, MAPs at 2 h after reinfusion (RE-120) were significantly lower than the baseline values ($p<.05$).

Vascular Reactivity

The pressure responses to the NE test are shown in Table 4. Before the induction of HS (NE-1), reactivity to NE of the M21 group was significantly higher than that of the other groups ($p<.05$). In the M100 group, reactivity to NE 2 h after reinfusion (NE-3) was significantly higher than to NE-1 and NE-2 ($p<.05$). In the M21 group, reactivity to NE after HS (NE-2) was significantly lower than to NE-1 ($p<.05$).

Table 1. Changes in total survivors

	Total survivors			
	HS-60	HS-120	RE-60	RE-120
M100	7/7	7/7[a]	6/7	6/7
M21	6/7	5/7	3/7	3/7
S100	7/7	7/7[a]	6/7	4/7
S21	6/7	3/7	3/7	3/7

HS-60, 60 min after induction of hemorrhagic shock (HS). HS-120, 120 min after induction of HS. RE-60, 60 min after reinfusion of shed blood (RE). RE-120, 120 min after RE. [a] $p<.05$ vs S21.

Table 2. Maximum shed blood volume during hemorrhagic shock

	M100	M21	S100	S21
shed blood (ml)	9.8 +/– 0.6	7.8 +/– 0.6	9.8 +/– 0.6	7.9 +/– 0.9

$p=.06$ between four groups. Values are mean ± SEM.

Table 3. Values for mean arterial pressure

		MAP			
		HS-0	RE-15	RE-60	RE-120
(torr)	M100	126 +/– 2[a]	100 +/– 11	81 +/– 9[b]	64 +/– 9[bc]
	M21	89 +/– 6	78 +/– 7	70 +/– 3	61 +/– 7[b]
	S100	122 +/– 3[a]	110 +/– 10	85 +/– 15	98 +/– 9
	S21	93 +/– 6	121 +/– 9	103 +/– 12	100 +/– 16
(kPa)	M100	17 +/– 0[a]	13 +/– 1	11 +/– 1[b]	8 +/– 1[bc]
	M21	12 +/– 1	10 +/– 1	9 +/– 0	8 +/– 1[b]
	S100	16 +/– 0[a]	15 +/– 1	11 +/– 2	13 +/– 1
	S21	12 +/– 1	16 +/– 1	14 +/– 2	13 +/– 2

MAP, mean arterial pressure. HS-0, before induction of hemorrhagic shock. RE-15, 15 min after reinfusion of shed blood (RE). RE-60, 60 min after RE; RE-120, 120 min after RE. [a] $p<.05$ vs M21 and S21. [b] $p<.05$ vs HS-0; [c] $p<.05$ vs RE-15. Values are mean ± SEM.

Table 4. Blood pressure responses to norepinephrine

	NE test (% change in MAP)		
	NE-1	NE-2	NE-3
M100	40 +/– 2	47 +/– 10	79 +/– 9[bc]
M21	106 +/– 10[a]	38 +/– 3[b]	80 +/– 16
S100	41 +/– 4	31 +/– 8	42 +/– 7
S21	66 +/– 22	43 +/– 7	80 +/– 0

NE, norepinephrine; MAP, mean arterial pressure. NE-1, NE test before induction of hemorrhagic shock. NE-2, NE test at 30 min after reinfusion of shed blood (RE). NE-3, NE test at 120 min after RE. [a] $p<.05$ vs M100, S100 and S21. [b] $p<.05$ vs NE-1; [c] $p<.05$ vs NE-2. Values are mean ± SEM.

Arterial Blood Gases

The changes in PaO_2, pH and $PaCO_2$ for the four groups are shown in Table 5. At all points of observation, the levels of PaO_2 in the M100 and S100 groups were significantly higher than those in the M21 and S21 groups ($p<.05$).

At HS-60, the pH of the M100 group was significantly lower than those of the other three groups ($p<.05$) and the pH of the M21 group was significantly lower than that of the S100 and S21 groups ($p<.05$). At HS-120 and RE-2, the pH's of the M100 and S100 groups were significantly lower than the baseline value ($p<.05$).

At HS-60, the level of $PaCO_2$ in the M100 group was significantly higher than those of the other groups ($p<.05$). After recovery from HS (RE-2), the $PaCO_2$ of the S100 group was significantly higher than those of the other groups ($p<.05$). At RE-15 and RE-120, the levels of $PaCO_2$ in the M100 and M21 groups were significantly lower than the baseline value ($p<.05$).

NO Derivatives

The changes in NOx concentration (μm/l) for the four groups are shown in Table 6. Before induction of HS, the NOx concentration of the S100 group was significantly higher than those of the other groups ($p<.05$).

Discussion

Although it may be clear that tissue oxygenation is affected by the inspired oxygen concentration [3], limited information is currently available concerning the use of higher oxygen concentrations and regulatory ventilation in experimental models of HS [3–5]. Therefore, we examined the effect of inspiratory oxygen concentration and the ventilation method on the survival rate, MAP, vascular reactivity to NE, the blood gas tension and NO derivatives before and after HS in the HS model.

In the present study, the animals that inspired air via spontaneous respiration during HS for two hours had a poor prognosis compared to the animals that inspired pure oxygen ($p<.05$). At 60 min after reinfusion, six of seven rats survived in the pure oxygen groups and three of seven rats survived in the air groups whether they were mechanically ventilated or not. Moreover, in animals that inspired pure oxygen, mechanical ventilation tended to lead to better results than spontaneous respiration at 120 min after reinfusion (6/7 vs 4/7). These findings were consistent with a previous study that demonstrated that oxygen significantly increased MAP and

Table 5. Values of arterial blood gases

	Group	HS-0	HS-60	HS-120	RE-2	RE-15	RE-120
pH	M100	7.41 +/- 0.01	7.18 +/- 0.02[bf]	7.24 +/- 0.06[f]	7.19 +/- 0.05[f]	7.30 +/- 0.06	7.39 +/- 0.05[gh]
	M21	7.43 +/- 0.02	7.27 +/- 0.03[c]	7.27 +/- 0.07	7.18 +/- 0.06[f]	7.24 +/- 0.08	7.47 +/- 0.02[h]
	S100	7.36 +/- 0.01[a]	7.33 +/- 0.01	7.22 +/- 0.04[f]	7.13 +/- 0.03[cfg]	7.23 +/- 0.03	7.33 +/- 0.02[h]
	S21	7.41 +/- 0.01	7.39 +/- 0.02	7.40 +/- 0.03	7.38 +/- 0.02	7.42 +/- 0.02	7.44 +/- 0.03
$PaCO_2$ (torr)	M100	44 +/- 1	50 +/- 2[b]	32 +/- 3[fg]	38 +/- 2[g]	31 +/- 3[fg]	28 +/- 2[fg]
	M21	40 +/- 3	38 +/- 3	24 +/- 2[fg]	33 +/- 2	28 +/- 2[f]	25 +/- 3[fg]
	S100	47 +/- 3	37 +/- 1	38 +/- 2[a]	48 +/- 3[dg]	44 +/- 3[e]	44 +/- 4[e]
	S21	43 +/- 2	34 +/- 0[f]	31 +/- 0[f]	34 +/- 3[f]	35 +/- 2[f]	34 +/- 2[f]
$PaCO_2$ (kPa)	M100	5.8 +/- 0.1	6.6 +/- 0.3[b]	4.2 +/- 0.4[fg]	5.1 +/- 0.3[g]	4.2 +/- 0.4[fg]	3.7 +/- 0.2[fg]
	M21	5.3 +/- 0.4	5.1 +/- 0.4	3.1 +/- 0.2[fg]	4.4 +/- 0.3	3.7 +/- 0.3[f]	3.3 +/- 0.4[fg]
	S100	6.2 +/- 0.4	4.9 +/- 0.1	5.1 +/- 0.2[a]	6.4 +/- 0.3[dg]	5.9 +/- 0.4[e]	5.8 +/- 0.5[e]
	S21	5.7 +/- 0.2	4.5 +/- 0.0[f]	4.1 +/- 0.0[f]	4.6 +/- 0.4[f]	4.6 +/- 0.2[f]	4.5 +/- 0.3[f]
PaO_2 (torr)	M100	362 +/- 17[i]	335 +/- 25[i]	288 +/- 36[i]	276 +/- 24[i]	274 +/- 39[i]	274 +/- 42[i]
	M21	68 +/- 6	70 +/- 6	84 +/- 9	59 +/- 7	59 +/- 8	55 +/- 7
	S100	325 +/- 35[i]	305 +/- 27[i]	319 +/- 20[i]	262 +/- 23[i]	309 +/- 33[i]	257 +/- 37[i]
	S21	58 +/- 2	66 +/- 9	78 +/- 7	75 +/- 13	70 +/- 8	72 +/- 7
PaO_2 (kPa)	M100	48 +/- 2[i]	45 +/- 3[i]	38 +/- 5[i]	37 +/- 3[i]	36 +/- 5[i]	36 +/- 6[i]
	M21	9 +/- 1	9 +/- 1	11 +/- 1	8 +/- 1	8 +/- 1	7 +/- 1
	S100	43 +/- 5[i]	41 +/- 4[i]	42 +/- 3[i]	35 +/- 3[i]	41 +/- 4[i]	34 +/- 5[i]
	S21	8 +/- 0	9 +/- 1	10 +/- 1	10 +/- 2	9 +/- 1	10 +/- 1

HS-0, before induction of hemorrhagic shock (HS). HS-60, 60 min after induction of HS; HS-120, 120 min after induction of HS. RE-2, two min after reinfusion of shed blood (RE); RE-15, 15 min after RE; RE-60, 60 min after RE; RE-120, 120 min after RE. [a] $p<.05$ vs M21; [b] $p<.05$ vs M21, S100 and S21; [c] $p<.05$ vs S21. [d] $p<.05$ vs M100, M21 and S 21; [e] $p<.05$ vs M100 and M21. [f] $p<.05$ vs HS-0; [g] $p<.05$ vs HS-60; [h] $p<.05$ vs RE-2. [i] $p<.05$ vs M21 and S21. Values are mean ± SEM.

Table 6. Values for total NOx (nitrite; NO_2^- + nitrate; NO_3^-)

	Total NOx (μmol/L)			
	HS-0	HS-120	RE-15	RE-120
M100	13.8 +/- 1.1	13.2 +/- 1.4	15.6 +/- 1.5	20.5 +/- 3.3
M21	10.7 +/- 0.7	12.6 +/- 1.3	8.4 +/- 1.4	17.2 +/- 0.0[b]
S100	14.4 +/- 2.1[a]	16.2 +/- 2.2	15.6 +/- 2.2	18.2 +/- 1.5
S21	8.7 +/- 1.0	10.3 +/- 2.6	9.7 +/- 2.5	13.1 +/- 3.7

HS-0, before induction of hemorrhagic shock (HS). HS-120, 120 min after induction of HS. RE-15, 15 min after reinfusion of shed blood (RE); RE-120, 120 min after RE. [a] $p<.05$ vs S21. [b] $p<.05$ vs RE-15. Values are mean ± SEM.

prolonged the survival of hemorrhaged rats (2). Although many experiments concerning HS have been carried out using rats in the past decades, inspiratory oxygen concentration was 21% under spontaneous respiration in almost all of those experiments [8–10]. According to the results of the present study, we may need to reevaluate the results obtained in those studies. In clinical practice, many patients suffering from HS are given supplemental oxygen and are supported by mechanical ventilation because tissue hypoxia plays an important role in the pathophysiology of circulatory shock [11]. Taking these facts into consideration, we consider that in experiments involving a rat HS model, oxygen and mechanical ventilation should be provided during HS.

The maximum shed blood volume tended to be greater in the pure oxygen groups than in the air groups ($p=.06$). This was mostly due to a maneuver by which we maintained HS at a definite MAP in this study. The oxygen

concentration affects the peripheral vascular resistance and changes the blood volume within the vessel [11–13]. The differences in the total volume of shed blood in the present study may have affected the magnitude of vascular dysfunction even though MAP was maintained at an equal value. MAP before HS was higher in the pure oxygen groups than in the air groups ($p<.05$). It has been established that oxygen inhalation increases MAP, and it has also been claimed that an increase in peripheral vascular resistance was the result of the hypertensive effect of oxygen [1]. Therefore, inspired oxygen concentration might have affected the volume of the shed blood in the present study. There are two types of HS models, either maintaining a predetermined MAP by withdrawing and infusing blood or withdrawing a predetermined volume of blood. The clinical relevance of a constant blood pressure protocol of HS has been a matter of debate [14]. But this method may be more desirable for comparing the effectiveness of treatments in each group of HS. It might be possible that the survival rates would be different if a standardized volume of shed blood is used as an end point of hemorrhagic shock.

HS induces vascular hyporesponsiveness to vasoconstrictor agents [15, 16]. In the present study, the vascular reactivity to NE was higher in the M21 group than in the other three groups before HS. In the pure oxygen groups, the vasoconstriction had already been brought about by the oxygenation [1] and the NE could not induce further more vasoconstriction. Comparing the percent change in MAP in air respiration groups, NE-2 values were less than the values in NE-1. During two hours of HS, hypoxemia might have been more prominent with air respiration than pure oxygen respiration. It has been shown that vascular hyporeactivity after HS is not due to changes in acidosis [17]. In this study, the pH decreased temporarily and increased over time, and the differences in pH were not statistically significant between the four groups at 15 min after reinfusion. In 6 of 19 rats, the pH was under 7.2 at 15 min after reinfusion, but the pH gradually increased in all cases. We performed the NE test of post HS at 30 min after reinfusion without correcting the acidosis by means of bicarbonate. The difference in vascular reactivity after HS was not statistically significant between the four groups. It seems that the pH did not affect the vascular reactivity in this study.

In our study, PaO_2 was maintained at about 60 mmHg in the S21 group, and respiratory arrest occurred in three of seven rats during HS. The results in HS experiments usually depend on the anesthetics used during the study [18]. It was also anticipated that the circulatory dynamics would be made unstable by the intermittent administration of anesthetics. Thus, in the present study, the anesthetic, pentobarbital, was given continuously so that it would not affect the circulatory dynamics. We used intravenous pentobarbital, which had similar results in the rat hemorrhage model without anesthesia [18]. Respiratory suppression due to continuous administration of pentobarbital may have been one of the causes of respiratory arrest and should be investigated as such. However, it may be a less likely cause than hypoxemia because the animals in the S100 group had a better survival rate, which was the same as that of the M100 group. In the present study, respiratory arrest was always followed by hypotension and bradycardia in the S21 group. Therefore, we concluded that hypoxia and low perfusion pressure during HS caused circulatory disturbance in the central nervous system. In our study, the difference in PaO_2 between the spontaneous respiration group and the mechanical ventilation group was not statistically significant. Therefore we concluded that mechanical ventilation was not an important factor in increasing the survival rate of the S21 group.

In the mechanical ventilation group, the pH decreased at one hour after the induction of HS. At two hours after induction of HS, the pH did not decrease because hyperventilation was performed in order to decrease the level of $PaCO_2$ in the latter half of HS. In the spontaneous respiration groups, compensatory hyperventilation occurred spontaneously in order to decrease the level of $PaCO_2$ and prevent the development of metabolic acidosis. On the other hand, it is possible that the compensatory hyperventilation was disturbed in the mechanical ventilation groups. Therefore, when a HS model is planned using mechanical ventilation, the ventilation needs to be adjusted in order to regulate the metabolic acidosis that occurs during long periods of HS as in the present study.

Two hours after reinfusion, mechanical ventilation decreased the $PaCO_2$ to less than 30 mmHg (4 kPa), and MAP was significantly lower than the baseline value in the mechanical ventilation groups. It may be possible that the hyperventilation that started one hour after HS might have decreased the venous return and caused hypotension to occur in this study.

NO is normally produced in endothelial cells by the constitutively present enzyme NO synthase (cNOS). NO has been shown to account for many of the actions attributed to endothelium-derived relaxing factor, which appears to play an important role as a modulator of blood flow in various tissues [19]. HS for 120 min caused a time-dependent reduction of the pressure responses to NE. This hyporeactivity might be mediated by an enhanced release of NO by cNOS [15]. Vascular decompensation following prolonged periods of HS was characterized by a failure of control animals to maintain arterial blood pressures. This progressive decrease in blood pressure was mediated by an enhanced formation of NO by inducible NOS after 150 min of HS [15]. In this study, NOx was higher in the pure oxygen group than in the air group before HS with spontaneous respiration. It has been suggested that NO production works to decrease the vascular tone that is constricted by pure oxygen inhalation [20]. In the C21 group, NOx increased at two hours after reinfusion ($p<.05$). These results indicate that increased production of NO is related to the vascular hyporesponsiveness to vasoconstrictor agents during the late stages of HS [21].

Conclusions

The inspiratory oxygen concentration and the ventilation method affect the survival rate and vascular reactivity of the rat hemorrhagic shock model. Selection of the inspiratory oxygen concentration and the ventilation method should be made according to the purpose of the individual hemorrhagic shock experiment.

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