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Effects of Hypotensive Anesthesia with Sodium Nitroprusside or Isoflurane on Hemodynamic and Metabolic Changes

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The hemodynamic and metabolic changes during induced hypotension with isoflurane (isoflurane group) or sodium nitroprusside (SNP group) were observed in twelve mongrel dogs. These hypotensive effects were evaluated at 30 and 60 minutes after the mean arterial blood pressure was lowered to 50% from the control. Hemodynamic changes were evaluated by measuring systemic arterial blood pressure, heart rate, central venous pressure, pulmonary capillary wedge pressure, cardiac output, systemic vascular resistance and pulmonary vascular resistance. Metabolic changes were evaluated by measuring serum lactate and pyruvate, arterio-venous oxygen content difference and oxygen extraction rate. We also compared the ventilatory effect of hypotensive anesthesia by blood gas analysis. The results were as follows: 1. Isoflurane inhalation 2-4 % or SNP infusion 10-20 μg/kg/min was required to reduce the mean arterial pressure to 50% of the control. 2. Heart rate was decreased slightly in the isoflurane group but significantly decreased in the SNP group. 3. There were no significant changes in central venous pressure and pulmonary capillary wedge pressure in either group. 4. Cardiac output was reduced in both groups but was more severe in the isoflurane group. 5. Systemic vascular resistance was decreased by 36% in the isoflurane group and 47% in the SNP group. 6. Acidosis was apparent and did not recover to the control until 30 minutes after recovery in the SNP group. 7. Arterio-venous oxygen difference was increased during hypotension in the isoflurane group probably due to decreased cardiac output. 8. The lactate/pyruvate ratio increased slightly in the SNP group. These results suggest that induced hypotension to 50% of the control with isoflurane may decrease cardiac output during hypotension but there was no evidence of tissue hypoxia or acidosis. But the SNP group revealed a decreased pH and an increased lactate/pyruvate ratio despite normal cardiac output, which may reveal the possibility of cyanide toxicity.

Key Words: Hypotension, isoflurane, nitroprusside, hemodynamics, metabolism

Since Gardner WJ (1946) lowered arterial pressure artificially by arteriotomy during neurosurgery in 1946, many techniques to induce hypotension such as high spinal anesthesia, deep inhalation anesthesia and techniques using hypotensive drugs such as ganglionic blockers, adrenergic blockers, nitroglycerine, adenosine, prostaglandin E_1, etc. have been introduced.

The main purpose of induced hypotension is to decrease blood loss, thereby decreaseing the need for blood transfusion and/or improving operating conditions at the surgical site (Vazeery and Lunde 1979; Sataloff *et al.* 1987; Sood *et al.* 1987). But Lindrop MJ (1975), Pascht and Huk (1986) reported that induced hypotension can produce many complications such as oliguria, cerebral thrombosis, retinal thrombosis, cardiovascular collapse, delayed awakening and cardiac arrest. Recently peripheral vasodilators have been used commonly as a hypotensive drug in induced hypotension in order to reduce hypotension-induced complications.

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Among peripheral vasodilators, sodium nitroprruside (SNP) is one of the most commonly used drugs because of its rapid onset, relatively consistent effect with minimal cardiac output change and short half life (Kreye 1980; Belmin 1990). Isoflurane, inhalation anesthetic agent, has gained increasing interest lately because of its rapid onset, ease of control, rapid recovery and ability to maintain the cardiac output relatively well (Lam and Gelb 1983; Eger 1984). But there is controversy about these results according to the authors because of the different degree and duration of induced hypotension.

The purpose of this study was to investigate the difference of hemodynamic and metabolic changes between SNP and isoflurane-induced hypotension in which the mean arterial blood pressure was lowered to 50% from the control for 30 and 60 minutes using twelve mongrel dogs.

MATERIALS AND METHODS

Twelve unpremedicated mongrel dogs weighing 13-15 kg were divided randomly into two groups as isoflurane group (n=7) and SNP group (n=5).

Anesthesia was induced with pentobarbital (25 mg/kg) intravenous injection and endotracheal intubation was performed with an 8 mm Portex® tube. After intubation, the dogs were paralyzed with pancuronium (0.08 mg/kg) and mechanical ventilation was adjusted to maintain $PaCO_2$ 35-45 mmHg with a Harvard® animal ventilator with tidal volume 10 ml /kg and respiratory rate 15-20/min. and the ventilator setting was kept unchanged throughout the study. Anesthesia was maintained with pentobarbital infusion (5 mg/kg/hr) during experimental preparation. Hypotension was induced with isoflurane inhalation (isoflurane group) or sodium nitroprusside infusion (SNP group).

Heart rate was measured by continuous electrocardiograpic monitoring and arterial blood pressure was monitored with a pressure transducer (Gould®) connected to the femoral arterial cannula (20 gauge Angiocath®) and 7.5 French sized Swan-Ganz catheter was introduced via the femoral vein. An internal jugular venous catheter was inserted with a 22 gauge Angiocath® for blood sampling to evaluate cerebral metabolic effect. Hartmann's solution was infused at the rate of 4 ml/kg/min throughout the entire experiment as a maintenance fluid. Body temperature was kept constant between 37 and 38℃ using the blanket during the experiment.

Central venous pressure and pulmonary capilliary wedge pressure were monitored via Swan-Ganz catheter and cardiac output was measured with Edward®) cardiac output computer (COM-1) using thermodilution technique.

Blood gas analysis of artery, mixed and internal jugular vein and metabolic parameters of lactate and pyruvate were measured. The following values were also calculated based upon the equations described below.

SVR (mmHg/1/min)=(MAP-CVP)/CO, PVR (mmHg/1/1min)=(PAP-PCWP)/CO, A-VDO_2 (ml/dl)=CaO_2-$C\bar{v}O_2$, A-VijDO_2 (ml/dl)=CaO_2-CvijO_2, Oxygen extraction rate=(CaO_2-$C\bar{v}O_2$)/CaO_2

SVR: systemic vascular resistance, PVR: pulmonary vascular resistance, MAP: mean arterial pressure, CVP: central venous pressure, CO: cardiac output, PAP: pulmonary arterial pressure, PCWP: pulmonary capillary wedge pressure, A-VDO_2: arterio-venous (mixed vein) oxygen content difference, A-VijDO_2: arterio-venous (internal jugular vein) oxygen content difference, CaO_2: arterial oxygen content, $C\bar{v}O_2$: venous (mixed) oxygen content, CvijO_2: internal jugular venous oxygen content.

Experimental parameters were measured when the blood pressure was stabilized after completion of experimental preparation as a control (phase I), 30 minutes after the mean arterial blood pressure was lowered to 50% from the control (phase II), 60 minutes after the mean arterial blood pressure was lowered to 50% from the control (phase III) and 30 minutes after the mean arterial blood pressure was recovered to more than 80% of the control (phase IV).

Statistical analysis was performed by the nonparametric Kruskal-Wallis procedure. A probability of 0.05 or less was considered a statistically significant difference.

RESULTS

Hypotension was induced smoothly within 5-10 minutes in both groups. The required doses for lowering and maintaining mean arterial blood pressure to 50% of the control were isoflurane 2-4% or SNP 10-20 μg/kg/min (mean 17 μg/kg/min). Heart rate was slightly changed in the isolurane group but was reduced significantly in the SNP group during hypotension. Central venous pressure and pulmonary capillary wedge pressure were not changed

significantly in both groups (Table 1).

Cardiac output was markedly reduced from 1.44 to 1.08 and 1.01 l/min at 30 and 60 minutes after hypotension in the isoflurane group. But it was reduced significantly only after 60 minutes of hypotension from 1.58 to 1.09 l/min in the SNP group. SVR was decreased to 63% (from 94.8 to 70.6 mmHg/l/min) during hypotension in the isoflurane group. But SNP decreased SVR to 53% (from 81.2 to 46.6 mmHg/l/min) during hypotension (Table 2).

Arterial pH did not change during hypotension in isoflurane group, but it was decreased during hypotension in the SNP group and did not return to

Table 1. Changes of mean arterial pressure, Heart rate, central venous pressure and pulmonary capillary wedge pressure Mean±SE

	Time	MAP (mmHg)	HR (rate/min)	CVP (mmHg)	PCWP (mmHg)
Isoflurane (n=7)	I	141±2.7	121±3.6	7.8±1.5	6.5±2.2
	II	78±1.1	110±6.8	8.3±1.9	7.3±1.6
	III	71±1.4	103±6.8	8.0±1.7	8.2±1.7
	IV	141±4.6	115±14	7.8±1.9	7.8±1.0
SNP (n=5)	I	135±1.5	116±4.2	8.6±1.7	11.4±1.3
	II	77±2.0	92±5.7	8.8±2.3	10.4±1.2
	III	76±1.5	94±6.3	8.6±1.7	12.4±1.9
	IV	135±1.3	98±8.5	11.8±1.1	11.8±1.1

Time I: control, II: 30 min. after experimental preparation, III: 60 min. after experimental preparation, IV: 30 min. after recovery

Table 2. Changes of cardiac output, systemic vascular resistance and pulmonary vascular resistance Mean±SE

		CO (l/min)	SVR (mmHg/l/min)	PVR (mmHg/l/min)
Isoflurane (n=7)	I	1.44±0.08	94.8±5.81	5.94±1.13
	II	1.08±0.14	73.3±1.22	6.21±1.78
	III	1.01±0.12*	70.6±9.95	3.88±0.37
	IV	1.49±0.07	92.2±6.19	5.76±1.33
SNP (n=5)	I	1.58±0.08	81.2±6.44	3.64±0.88
	II	1.46±0.05	46.6±1.11*	5.10±1.59
	III	1.09±0.04*	62.1±3.17*	4.66±089
	IV	1.54±0.11	83.5±6.80	5.22±1.39

$p<0.05$ as compared to the control

Table 3. Changes of blood gas analysis Mean±SE

	Isoflurane (n=7)					SNP (n=5)				
	pH	PO_2 (mmHg)	PCO_2 (mmHg)	HCO_3^- (mEq/l)	BE (mEq/l)	pH	PO_2 (mmHg)	PCO_2 (mmHg)	HCO_3^- (mEq/l)	BE (mEq/l)
Artery										
I	7.39±0.04	565±17	36±2.5	21.7±0.6	-3.2±0.05	7.38±0.03	529±23	36±1.4	21.7±0.6	-4.4±0.46
II	7.36±0.03	460±70	36±3.2	20.8±0.4	-3.2±0.61	7.30±0.01*	524±7	42±1.1	20.8±0.4	-4.4±0.65
III	7.36±0.28	541±26	37±2.9	21.1±0.4	-3.3±0.43	7.29±0.01*	530±8	38±4.6	21.1±0.4	-5.9±1.33
IV	7.35±0.26	588±22	39±2.9	21.6±0.7	-3.3±0.72	7.30±0.01*	561±20	41±2.1	21.6±0.7	-4.6±0.52
Mixed Vein										
I	7.34±0.10	66±7.0	41±2.9	21.6±0.7	-3.3±0.65	7.31±0.01	67±3.2	42±1.5	21.6±0.7	-3.7±0.62
II	7.34±0.08	48±2.8*	39±3.4	21.5±0.5	-3.3±0.91	7.23±0.01*	67±7.4	45±1.8	21.5±0.5	-5.8±0.82
III	7.31±0.76	48±1.6*	42±3.9	21.4±0.6	-3.8±0.21	7.24±0.01*	64±5.7	46±4.9	21.4±0.6	-6.1±1.60
IV	7,33±0.78	66±9.1	40±2.6	21.3±0.2	-3.6±0.83	7.24±0.01*	68±6.7	60±3.0	21.3±0.2	-5.9±0.97
Int. Jug. Vein										
I	7.31±0.01	78±6.6	44±1.9	22.7±0.7	-2.8±0.57	7.30±0.01	75±5.8	44±4.7	22.7±0.7	-4.2±0.78
II	7.31±0.29	76±9.9	41±1.5	20.8±0.4	-4.4±0.38*	7.24±0.01	75±3.6	50±1.9	20.8±0.4	-4.9±0.89
III	7.29±0.01	75±4.4	44±3.1	21.4±0.8	-4.3±0.44*	7.26±0.02	78±3.1	49±3.3	21.4±0.8	-4.7±0.45
IV	7.28±0.01	76±7.5	47±2.8	22.2±0.7	-3.9±0.41	7.25±0.01	72±3.1	46±3.5	22.2±0.7	-6.2±1.11

*$P<0.05$ as compared to the control (I)

Table 4. Metabolic changes of hypotension **Mean ± SE**

	Isoflurane (n=7)				SNP(n=5)			
	I	II	III	IV	I	II	III	IV
$AVDO_2$	3.89±0.42	3.50±0.59	5.54±0.37	3.74±0.68	3.62±0.28	3.55±0.59	4.15±0.73	3.88±0.54
$AVijDO_2$	2.71±0.47	3.50±0.70	3.22±0.29	2.87±0.52	3.02±0.37	2.71±0.35	2.84±0.20	3.31±0.27
O_2 extract rate	0.18	0.24	0.25	0.16	0.16	0.16	0.29	0.17
Mixed Vein								
lactate (mg/dl)	20.5±5.17	23.9±3.33	24,5±3.08	20.1±4.17	22.7±0.76	25.7±3.84	24.4±6.14	29.6±3.22
pyruvate (mg/dl)	0.62±1.11	0.83±1.12	0.80±1.13	0.85±1.15	0.78±0.07	0.69±0.08	0.72±0.15	0.77±0.17
L/P ratio	33	28	31	24	29	32	43	25
Int. Jug. Vein								
lactate (mg/dl)	27.0±5.17	30.6±4.5	23.1±3.90	23.8±4.62	23.7±5.55	29.3±4.73	36.3±3.70	29.6±3.22
puruvate (mg/dl)	0.76±0.13	0.68±0.13	0.74±0.14	0.66±0.10	0.56±0.42	0.69±0.08	0.72±0.15	0.77±0.17
L/P ratio	36	45	32	37	42	52	50	38

$AVDO_2$: arterio-venous (mixed vein) oxygen content difference
$AVijDO_2$: arterio-venous (internal jugular vein) oxygen content difference

the control even after 30 minutes of recovery. Arterial oxygen and carbon dioxide tension were not changed in both groups.

Oxygen tension of mixed vein was reduced significantly after 30 and 60 minutes of hypotension only in the isoflurane group. Base deficits were greater during hypotension in SNP than in the isoflurane group (Table 3).

The metabolic effects were summarized in table 4. Plamsa lactate and pyruvate levels were not changed significantly in either group but lactate/pyruvate (L/P) ratio revealed a tendency to increase during hypotension especially in the SNP group. $AVDO_2$ and oxygen extraction rate were increased after 60 minutes of hypotension in the isoflurane group but not in the SNP group.

DISCUSSION

Since Johnson CC (1929) administered SNP to a human patient, SNP rapidly gained acceptance as a major hypotensive agent (Page 1951; Taylor *et al.* 1970) because of its rapid, transient and potent action. In contrast to other vasodilators in common use today SNP does not appear to have marked action on any systemic organ other than the vascular bed, and consequently the return to normotension is pleasantly free from residual side effects (Enderby and Eckenhoff 1985). Moderate tachycardia is common in SNP-induced hypotension because of intact baroreceptor response (Wildsmith *et al.* 1973; Fahmy *et al.* 1989). Therefore SNP has the advantage of not reducing cardiac output despite hypotension. But in prolonged use, it can produce tachyphylaxis by stimulating the sympathetic nerve system and the renin-angiotensin system. Tachyphylaxis demands a large dose of SNP to maintain the hypotensison constantly. Overloading of SNP may cause an accumulation of free cyanide ions by SNP metabolism. Free cyanide ions combine with mitochondrial cytochrome oxidase and impair aerobic cellular respiration, and ultimately leads to metabolic acidosis and death (Aitken *et al.* 1977; Buchwald A, 1989). Therefore, it is recommended not to exceed 1.5 mg/kg for short administration (Vesey *et al.* 1982) or infusion rate above 10 μg/kg/min (Michenfelder and Thinker 1977).

Isoflurane, which is a recently introduced inhalation anesthetic agent, is a halogenated methyl-ethyl ether and an isomer of enflurane. Its cardiovascular effects resemble those of halothane and enflurane.

However the major features which distinguish it from halothane and enflurane are that it has rapid onset and recovery, more potent peripheral vasodilating effect and can maintain cardiac function relatively well. It also has the ability to protect the brain from hypoxia due to decrease in cerebral metabolic rate (Artru 1984; Michenfelder *et al.* 1987). With these advantages, isoflurane has been gaining increasing interest recently as a hypotensive agent in induced hypotension.

In our study, mean arterial blood pressures were

rapidly lowered to 50% from the control within 5-10 minutes with inspired isoflurane concentration 2-4% or SNP infusion 10-20 μg/kg/min. There were no significant changes in central venous pressure and pulmonary capillary wedge pressure during hypotension in either group due to the minimal effect on pulmonary vasculature of these drugs under normoxic condition (Colley *et al.* 1979; Miller RD, 1986).

Cardiac output was reduced during hypotension in the isoflurane group but it was reduced only after 60 minutes of hypotension in the SNP group. This is not consistent with other reports that cardiac output is maintained well with isoflurane anesthesia, because we used a high concentration (2-4%) instead of the usual anesthetic concentration (1-2%) in order to produce profound hypotension. And our observation is similar to that of Priebe H (1987) that an isoflurane inhalation concentration above 1.8% could produce myocardial depression in dogs. Our result of decreased cardiac output after 60 minutes of hypotension in the SNP group is in contrast to the generally known SNP characteristic of having no myocardial depressive effect. But this may be explained partly by the report of Thinker JH and Michenfelder JD (1978) that administration of SNP with a dose of 10-20 μg/kg/min can produce cyanide toxicity after 60-70 minnutes resulting in reduced heart rate and cardiac output. Systemic vascular resistance was not decreased significantly but showed a tendency to decrease during hypotension in the isoflurane group. But in the SNP group, systemic vascular resistance was significantly decreased during hypotension because of the more potent direct vasodilating property of SNP. Change of heart rate was minimal in the isoflurane group because isoflurane maintains baroreceptor reflex relatively well compared to other inhalation anesthetics (Kotorly *et al.* 1984). But in contrast to other reports heart rate was reduced significantly during hypotension in the SNP group, which may reflect the possibility of cyanide toxicity though we did not measure plasma free cyanide level.

Blood gas analysis did not reveal significant changes of carbon dioxide tension and bicarbonate in either group. But the pH of arterial and mixed venous blood was significantly reduced during hypotension in the SNP group, even though oxygen tension of mixed vein was not reduced and elevation of $AVDO_2$ or oxygen extraction rate were not apparent. We suspect these results were due to depression of aerobic metabolism in the tissue by cyanide toxicity.

Isoflurane is known to have an effect on brain protection from hypoxic insult by decreasing cerebral metabolic rate. But there was not any difference between the two groups in either the internal jugular venous blood gas analysis or the lactate/pyruvate ratio in our study. Lactate and pyruvate, primarily originated from the cytoplasmic glycolytic pathway, can pass freely through the cell membrane. Therefore lactate and the L/P ratio in the blood can be taken as an index reflecting intracellular lactate and the intracellular L/P ratio (Krebs HA, 1967). There were minimal changes in lactate and pyruvate in mixed venous blood in both groups, but the L/P ratio revealed a tendency to increase during hypotension only in the SNP group which also may reflect the metabolic acidosis.

With the above results we can conclude that an isoflurane inhalation of 2-4% or an SNP infusion of 10-20 μg/kg/min was required to lower the mean arterial blood pressure to 50% of the control. In contrast to SNP induced hypotension, isoflurane induced hypotension decreased cardiac output with a relatively small decrease in systemic vascular resistance and this may be due to isoflurane induced myocardial depression. But there was no evidence of metabolic acidosis in the isoflurane group. SNP induced hypotension decreased systemic vascular resistance significantly with a slight decrease in cardiac output. We consider these effects to possibly be due mainly to peripheral vasodilation rather than myocardial depression. But metabolic acidosis, even in the recovery phase, despite near normal cardiac output and heart rate in the SNP group could suggest the possibility of cyanide toxicity.

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