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Cardiovascular Actions of Nitrous Oxide or Halothane in Hypovolemic Swine

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During normovolemia, nitrous oxide causes mild sympathetic stimulation and direct myocardial depression; these effects offset each other, resulting in only minimal cardiovascular changes. To test the hypothesis that during hypovolemia this balance would change and depression predominate, 10 swine were made hypovolemic (30% blood loss) and then were given 70% N_2O (0.25 MAC in swine) or an equipotent concentration of halothane, an agent that does not cause sympathetic stimulation. The alternate anesthetic was given to the same hypovolemic swine on another day. Five minutes after induction of anesthesia during hypovolemia, both N_2O and halothane caused significant, physiologically important deterioration of compensation for hemorrhage. Halothane decreased systemic vascular resistance (SVR); N_2O was more variable in its action, and SVR did not decrease significantly. Both agents caused similar decreases in cardiac output, mean aortic blood pressure, stroke volume, oxygen consumption, and left ventricular minute work, despite increases in plasma epinephrine concentration and plasma renin activity. No differences were found between groups for any of these variables ($P > 0.05$). Plasma norepinephrine concentration increased only in the N_2O group and was greater in that group than in the halothane group. The deterioration of cardiovascular compensation for hemorrhage was expressed metabolically by similar decreases in the two groups in partial pressure of oxygen of mixed venous blood and by increases in blood lactate concentration. Thirty minutes after induction of anesthesia, with stable end-tidal anesthetic concentrations, both groups had some cardiovascular, but no metabolic, recovery. Oxygen tension of mixed venous blood and blood lactate concentrations continued to be similar in the two groups. The authors conclude that administration of N_2O in hypovolemic swine results in cardiovascular depression that is not different from that caused by halothane, an anesthetic having no sympathetic properties. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, volatile: halothane. Blood: loss; hemorrhage. Polypeptides: renin-angiotensin. Sympathetic nervous system: catecholamines; epinephrine; norepinephrine.)

ALTHOUGH HYPOVOLEMIA should be corrected before induction of anesthesia, complete restoration of blood volume is not always possible. Anesthetics such as cyclopropane and ketamine, which produce hypertension during normovolemia,[1,2] have been advocated by some for use in hypovolemic patients. To examine the interaction of hemorrhage with anesthetic drugs, investigators usually first anesthetize animals and then remove blood. When this procedure was followed, dogs that were bled while anesthetized with cyclopropane had a lower survival rate than did dogs that were bled while anesthetized with other anesthetics.[3] Other studies of dogs[4] and rats[5–7] bled during ketamine anesthesia have produced differing interpretations regarding the usefulness of this drug during hypovolemia.

However, the interaction of anesthetics and hemorrhage may differ when hypovolemia precedes induction of anesthesia. Few controlled investigations have examined the effects of anesthetic agents when used for induction of anesthesia in unmedicated hypovolemic humans or animals. Recently, when inducing anesthesia in hypovolemic swine, we found no differences in the cardiovascular responses to either ketamine or thiopental, despite a very large increase in circulating catecholamines after administration of ketamine.[8]

Nitrous oxide also has been used during hypovolemia. It is a good analgesic and has mild sympathomimetic properties.[9] At 1.0 MAC in normovolemic humans, hyperbaric nitrous oxide anesthesia results in no cardiovascular changes‡; only minimal cardiovascular changes appear when nitrous oxide is added to inhaled anesthetics[10,11] or when N_2O administered with an inhaled anesthetic[12,13] is compared with inhaled anesthetics given without N_2O.[14,15] At these anesthetic levels the direct myocardial depressant action of N_2O[16,17] is likely offset by the indirect sympathetic stimulation produced by N_2O.[18] However, the actions of N_2O during hypovolemia have not been studied. We suspected that the effects of nitrous oxide during hypovolemia would not be similar to those reported by others during normovolemia; that in the presence of sympathetic stimulation occurring with hemorrhage, there would be minimal or no response to the additional sympathomimetic actions of nitrous oxide; and that any such response would be overwhelmed by the cardiovascular depressant properties of nitrous oxide. We reasoned that, therefore, no cardiovascular or metabolic differences would be found when nitrous oxide was compared with an anesthetic not having sympathomimetic properties. We tested this hypothesis by comparing the

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‡ Winter PM, Hornbein TF, Smith G: Hyperbaric nitrous oxide anesthesia in man: Determination of action of anesthetic potency (MAC) and cardiorespiratory effects. Abstracts of Scientific Papers, Annual Meeting of the American Society of Anesthesiologists, 1972, p 103.

cardiovascular and metabolic sequelae of inducing anesthesia with equipotent concentrations of N_2O or halothane in hypovolemic swine.

Materials and Methods

Approval for this experimentation was obtained from the Committee on Animal Research at the University of California, San Francisco. We studied 10 young swine (Chester-White-Yorkshire cross-breed, weight 21.2 ± 0.9 kg, mean ± SE) twice each. Animals were anesthetized briefly with halothane in oxygen and nitrogen (which was adjusted to keep Pa_{O_2} at 150–200 mmHg) and paralyzed with succinylcholine, 2 mg/kg iv (later followed by administration of metocurine, 0.2 mg/kg iv, supplemented as required). The trachea was intubated and ventilation controlled (tidal volume, 20 ml/kg; frequency was adjusted to keep Pa_{CO_2} at 38.0 ± 0.4 mmHg throughout the study). After local infiltration with 0.25% bupivacaine, catheters were inserted through the superficial femoral artery into the abdominal aorta and percutaneously through the innominate vein into the pulmonary artery.

Halothane then was discontinued and eliminated by ventilation until its end-tidal concentration, measured by mass spectroscopy (Perkin-Elmer Model MGA 1100AB®), decreased to less than 0.24 mmHg (0.025 MAC).[19] We waited an additional 30 min before beginning our studies.

Systemic arterial, pulmonary arterial, and right atrial pressures were transduced (Statham 23Db®); and mean pressures were derived with the use of a Gould preamplifier. Cardiac output was estimated with a thermodilution technique (injectate was 3 ml of 0.9% NaCl) at a continuously measured temperature of 0° C), a thermistor-tipped 5-Fr pulmonary arterial catheter (Edwards Laboratories), and an analog computer (Edwards Model 9520A®). Cardiac output was measured until two successive values produced satisfactory logarithmic washout curves and differed by no more than 0.2 l/min. Partial pressures of oxygen, carbon dioxide, halothane, and nitrous oxide were measured continuously in the center of the orifice of the endotracheal tube with the use of mass spectroscopy and were recorded by polygraph (Gould Model 2800®). Temperature, measured in pulmonary arterial blood, was kept within 0.5° C of its initial value using circulating water heating pads.

We calculated systemic vascular resistance (SVR) as the difference between mean aortic (BPa) and right atrial pressures, divided by cardiac output. Pulmonary vascular resistance was calculated as the difference between mean pulmonary arterial and pulmonary arterial wedge pressures, divided by cardiac output.

During each experimental condition, we measured *p*H and partial pressures of oxygen and carbon dioxide in aortic and pulmonary arterial blood using appropriate electrodes. Oxygen concentrations in systemic and pulmonary arterial blood were measured in duplicate using a galvanic cell instrument (Lex-O_2-Con-TL®, Lexington Instruments). We calculated oxygen consumption as the product of cardiac output and the difference between arterial and mixed venous oxygen concentrations. Base-excess was estimated with the use of a nomogram for swine blood.[20]

During each experimental condition, arterial blood samples were obtained for enzymatic measurement of whole blood lactate concentrations[21] and plasma epinephrine and norepinephrine concentrations,[22] and for radioimmunoassay of plasma renin activity.[23]

All of these measurements and calculations were made while animals were normovolemic. Then animals were made hypovolemic by removing 30% of the estimated blood volume[24] through the arterial cannula over 30 min. After 30 additional min, variables were measured again.

Each animal then was given, in random order, either 0.25 MAC N_2O (70%) or 0.25 MAC halothane (0.31%), according to our previously determined MAC values in swine for these agents.[19] In all other respects, animals were treated similarly. The other anesthetic was administered to each animal at least a week later (range: 7–17 days). All animals were in good health and behaved in a similar manner on both occasions.

All measurements were repeated 5 and 30 min after stable end-tidal concentrations of anesthetic were achieved. Shed blood then was infused into the animal, and measurements were repeated 30 min later. We then discontinued the anesthetic agent, and measurements were repeated after the anesthetic concentration had decreased to less than 0.03% halothane or 3% N_2O but not sooner than 60 min after completion of the blood transfusion.

For each experimental condition, differences between the two sets of data (N_2O and halothane) were compared using Student's *t* test for paired statistics, analysis of variance with repeated measures, and the Newman-Keuls method of multiple comparisons.[25] Because the nitrous oxide and halothane groups did not differ in the awake normovolemic condition or in their responses to hypovolemia, data for the two groups were combined. Then, differences between the awake normovolemic and hypovolemic states were compared with the use of Student's *t* test for paired statistics. Because of large interanimal variability in plasma epinephrine and norepinephrine concentrations, and renin activity following induction of anesthesia during hypovolemia, these values were converted to per cent of the unmedicated, hypovolemic values before statistical analysis. Differences between states within a group were compared using analysis of variance with repeated measures and the Newman-Keuls method of multiple comparisons.[25]

To determine whether the cardiovascular actions of low concentrations of anesthetic given to hypovolemic swine differed from the cardiovascular actions of similar anesthetic concentrations in normovolemic swine, we examined data from another five swine (19.9 ± 0.7 kg) while awake and while given 0.3 MAC end-tidal halothane. Procedures were similar to those described above for the first group of ten animals, except that this second group of five swine was not bled. We chose to administer 0.3 MAC halothane rather than 0.25 MAC to compensate for the approximately 20% decrease in MAC for halothane during hemorrhagic hypotension.[26]

Data obtained from this group while animals were awake was compared with data from the same group given 0.3 MAC halothane, using Student's *t* test for paired statistics.

For all analyses, statistical significance was accepted when $P < 0.05$. All values are presented as mean ± SE.

Results

Hemorrhage

Animals responded to hemorrhage (table 1), as in our earlier study.[8] Cardiac filling pressures decreased. Plasma renin activity, plasma concentrations of epinephrine and norepinephrine, heart rate, and systemic vascular resistance increased. Stroke volume, cardiac output, and mean aortic blood pressure decreased. Oxygen consumption increased and partial pressure of oxygen in mixed venous blood ($P\bar{v}_{O_2}$) decreased. A decrease in base-excess and an increase in whole blood lactate concentration indicated systemic acidosis. The response to hemorrhage was similar on both experimental days; no differences were found between the data for the two groups for any variable during normovolemia or after hemorrhage before induction of anesthesia.

Induction of Anesthesia

Although we attempted to keep Pa_{O_2} at similar levels in the two groups, Pa_{O_2} differed significantly after induction of anesthesia (100 ± 3 mmHg for nitrous oxide and 160 ± 12 mmHg for halothane) ($P < 0.001$). However, this difference was probably not physiologically important: no animal was hypoxic. The lowest Pa_{O_2} was 82 mmHg, which we calculated to have resulted in an oxyhemoglobin saturation of more than 95%. Because hematocrit was slightly higher after administration of the anesthetic agent in the N_2O group (30% ± 1% *vs.* 27% ± 3%) ($P > 0.05$), the resulting arterial oxygen content for the N_2O group was actually greater (but not significantly) than in the halothane group (12.8 ± 0.6 ml/dl for nitrous oxide and 12.1 ± 0.4 ml/dl for halothane).

TABLE 1. Awake Swine Response to 30% Hemorrhage

Variable	Normovolemia	Hypovolemia
Right atrial pressure (mmHg)	0.9 ± 0.3	−0.4 ± 0.3*
Pulmonary wedge pressure (mmHg)	2.4 ± 0.3	0.1 ± 0.3*
Heart rate (beats/min)	128 ± 6	182 ± 9*
Mean aortic blood pressure (mmHg)	133 ± 3	100 ± 5*
Pulmonary artery pressure (mmHg)	13.6 ± 0.5	9.2 ± 0.6*
Cardiac output ($ml \cdot min^{-1} \cdot kg^{-1}$)	192 ± 5	121 ± 5*
Stroke volume (ml/kg)	1.55 ± 0.07	0.70 ± 0.05*
Oxygen consumption ($ml \cdot min^{-1} \cdot kg^{-1}$)	7.74 ± 0.27	8.75 ± 0.37‡
Blood lactate (mmol/l)	1.12 ± 0.14	1.56 ± 0.16†
Base excess (mmol/l)	4.4 ± 0.4	2.5 ± 0.5*
Plasma epinephrine (pg/ml)	338 ± 39	744 ± 76*
Plasma norepinephrine (pg/ml)	307 ± 40	629 ± 116‡
Plasma renin activity (ng AI $\cdot ml^{-1} \cdot h^{-1}$)	9.1 ± 2.2	19.0 ± 3.0*
Systemic vascular resistance ($mmHg \cdot l^{-1} \cdot min \cdot kg$)	694 ± 23	837 ± 40†
Pulmonary vascular resistance ($mmHg \cdot l^{-1} \cdot min \cdot kg$)	58.8 ± 2.2	76.6 ± 5.3†
Mixed venous oxygen tension (mmHg)	51 ± 1	38 ± 1*

Values are mean ± SE. n = 10 per group.
* $P < 0.001$.
† $P < 0.01$.
‡ $P < 0.05$.

Data for cardiovascular and metabolic variables 5 and 30 min after administration of anesthetic are given in table 2.

Five minutes after stable end-tidal concentrations of halothane or nitrous oxide were achieved, there were no changes in left- or right-sided cardiac filling pressures or differences between the two groups ($P > 0.05$) for these variables. Substantial changes occurred in plasma concentrations of vasoactive agents. Plasma epinephrine concentrations and renin activity increased in both groups ($P < 0.05$) and did not differ between groups ($P > 0.05$). Plasma norepinephrine concentration did not change with halothane ($P > 0.05$) but increased with N_2O ($P < 0.05$), resulting in a significant difference between the two groups. Despite these increases, on all but two occasions, SVR decreased with induction of anesthesia. Systemic vascular resistance and consequently BPa varied more when animals were given N_2O than when they were given halothane. Whenever animals were given halothane, and when eight of the 10 animals were given N_2O, SVR and BPa decreased. Two swine had increases in SVR and BPa 5 min after administration of N_2O. Swine given halothane had significant decreases in SVR ($P < 0.05$) and in BPa

TABLE 2. Cardiovascular and Metabolic Variables Five and Thirty Minutes after Administration of 0.25 MAC Halothane or Nitrous Oxide to Hypovolemic Swine

Variable	5 Min		30 Min	
	Halothane	N_2O	Halothane	N_2O
Anesthetic concentration (%)	0.31 ± 0.004	69.6 ± 0.2	0.31 ± 0.004	70.0 ± 0.3
Right atrial pressure (mmHg)	0.6 ± 0.6	−0.1 ± 0.4	−0.3 ± 0.4	0.5 ± 0.6
Pulmonary wedge pressure (mmHg)	0.7 ± 0.5	0.7 ± 0.5	0.8 ± 0.4	1.4 ± 0.6
Heart rate (beats/min)	157 ± 15	191 ± 18*	154 ± 15	207 ± 14†
Mean aortic blood pressure (mmHg)	39 ± 6	62 ± 10	56 ± 6	86 ± 7*
Cardiac output ($ml \cdot min^{-1} \cdot kg^{-1}$)	63 ± 6	84 ± 11	105 ± 10	111 ± 7
Stroke volume (ml/kg)	0.42 ± 0.04	0.45 ± 0.05	0.71 ± 0.06	0.55 ± 0.03*
Oxygen consumption ($ml \cdot min^{-1} \cdot kg^{-1}$)	5.85 ± 0.48	7.20 ± 0.71	7.60 ± 0.57	8.86 ± 0.60*
Blood lactate (mmol/l)	2.88 ± 0.45	2.28 ± 0.26	3.52 ± 0.42	2.84 ± 0.49
Base excess (mmol/l)	2.6 ± 0.8	3.3 ± 0.7	1.6 ± 0.6	1.9 ± 0.9
Plasma epinephrine‡	489 ± 146	272 ± 90	187 ± 36	189 ± 65
Plasma norepinephrine‡	86 ± 15	188 ± 32*	77 ± 16	194 ± 37*
Plasma renin activity‡	244 ± 56	193 ± 31	203 ± 38	168 ± 35
Systemic vascular resistance ($mmHg \cdot l^{-1} \cdot min \cdot kg$)	616 ± 69	724 ± 58	549 ± 42	765 ± 49*
Pulmonary vascular resistance ($mmHg \cdot l^{-1} \cdot min \cdot kg$)	112 ± 13.8	98.7 ± 13.9	74.7 ± 4.1	87.1 ± 8.4
Mixed venous oxygen tension (mmHg)	26 ± 1	29 ± 2	32 ± 1	32 ± 1

Values are mean ± SE. n = 10 per group.

* $P < 0.05$, † $P < 0.001$ between groups at similar times after anesthetic administration. Absence of symbol indicates difference not statistically significant except for anesthetic concentration.

‡ Plasma epinephrine, norepinephrine, and renin activity are expressed as percentages of unmedicated, hypovolemic values.

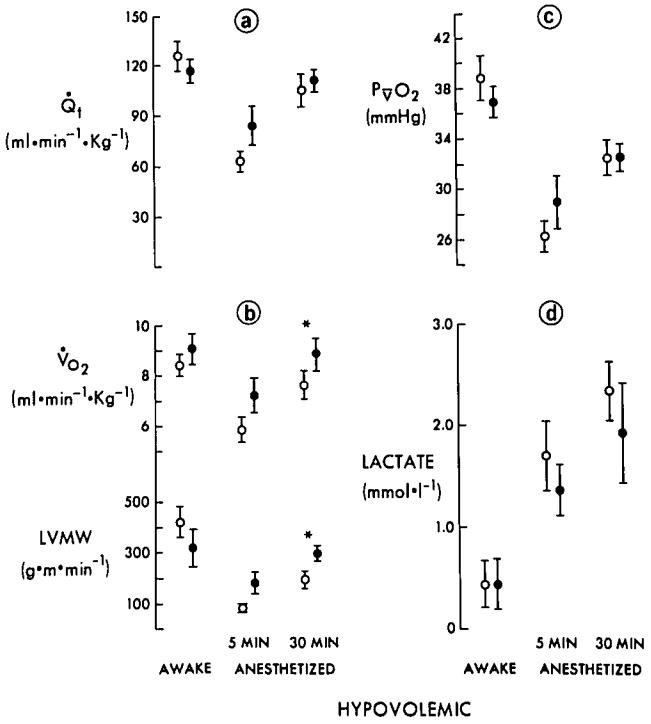

FIG. 1. Mean values (±SEM) for the following: *A.* Cardiac output ($\dot{Q}_t$). *B.* Oxygen consumption ($\dot{V}_{O_2}$) and left ventricular minute work (LVMW). *C.* Partial pressure of oxygen in mixed venous blood ($P\bar{v}_{O_2}$). *D.* Change from awake normovolemic values for blood lactate concentration in two groups of 10 awake hypovolemic swine 5 and 30 min after induction of anesthesia with either 0.25 MAC halothane (○) or N_2O (●). *Groups differed significantly ($P < 0.05$).

($P < 0.05$) (fig. 1). BPa also decreased in the N_2O group ($P < 0.05$). However, because of the variability in the N_2O group 5 min after induction of anesthesia, the decrease in SVR was not statistically significant, nor were differences in SVR or BPa found between groups. Both anesthetics decreased cardiac output, and no difference was found between nitrous oxide and halothane (fig. 1). Heart rate was significantly higher after induction with N_2O than with halothane. Stroke volume decreased similarly with both anesthetics and did not differ between groups. Deterioration of cardiovascular compensation for hemorrhage resulted in similar metabolic consequences in the two groups. Oxygen consumption and $P\bar{v}_{O_2}$ decreased significantly and similarly in both groups and did not differ between groups (fig. 1). Also, no difference in blood lactate concentration was evident between the halothane group and the nitrous oxide group (fig. 1).

Thirty minutes after induction of anesthesia, with stable end-tidal anesthetic concentrations of halothane or nitrous oxide, both groups showed some cardiovascular, but no metabolic, recovery. Pulmonary artery wedge pressure did not change or differ between groups. Relationships between the two groups for plasma vasoactive agents did not change. Plasma norepinephrine concentration and plasma renin activity did not change for either group. Plasma epinephrine concentration decreased significantly only in the halothane group. Plasma epinephrine concentration and renin activity still did not differ between the two groups, and plasma norepinephrine concentration

continued to be greater when the animals were given N_2O (1,373 ± 401 pg/ml) than when they were given halothane (422 ± 80 pg/ml) ($P < 0.05$). Some cardiovascular recovery occurred during the 25-min period. Although SVR did not change significantly in either group, its variability decreased in the N_2O group, and SVR was now greater when the swine were given N_2O than when they were given halothane ($P < 0.02$). BPa increased significantly in both groups; variability for BPa in the N_2O group also had diminished, and BPa was now significantly greater in the N_2O group than in the halothane group ($P < 0.02$). Cardiac output increased in both groups ($P < 0.05$) to similar values ($P > 0.05$) (fig. 1). Heart rate did not change in either group ($P > 0.05$) and continued to be greater in the N_2O group than in the halothane group ($P < 0.001$). During this 25-min period, stroke volume increased with halothane ($P < 0.05$) but not with N_2O, resulting in a significant difference between the two groups. Oxygen consumption paralleled left ventricular minute work (fig. 1) and increased in both groups ($P < 0.05$) but was significantly greater when the animals were given N_2O than when they were given halothane. Oxygen partial pressure in mixed venous blood increased significantly and similarly in both groups and did not differ between groups (fig. 1). However, blood lactate concentration in the two groups continued to increase similarly (0.56 ± 0.33 mmol/l for nitrous oxide and 0.64 ± 0.22 mmol/l for halothane) ($P > 0.05$) (fig. 1).

Return of Shed Blood

Thirty minutes after return of shed blood, plasma epinephrine and norepinephrine concentrations were greater and $P\bar{v}_{O_2}$ was less when animals were given N_2O rather than halothane ($P < 0.05$) (table 3). No significant differences were found between the groups for any other variable.

After elimination of anesthetic agents, the two groups did not differ for any variable; also, no differences were found for any variable, in either group, between the start and end of the experiment (*i.e.*, for both states awake, normovolemic). All animals survived 24 h.

Normovolemic Animals

Given to normovolemic animals, 0.3 MAC halothane decreased mean aortic blood pressure but did not alter left- or right-heart filling pressures, heart rate, cardiac output, systemic vascular resistance, or mean pulmonary artery blood pressure (table 4).

Discussion

The cardiovascular and metabolic effects of N_2O or halothane during hypovolemia differ from those reported during normovolemia and those we observed for halothane during normovolemia. In normovolemic humans and animals, N_2O causes direct myocardial depression and central sympathetic stimulation.[27] The net result in intact animals depends on several factors, such as the concen-

Table 3. Cardiovascular and Metabolic Values after Return of Shed Blood in Swine Anesthetized with 0.25 MAC Halothane or 0.25 MAC N_2O

Variable	Halothane	Nitrous Oxide
Right atrial pressure (mmHg)	1.8 ± 0.8	2.0 ± 0.9
Pulmonary wedge pressure (mmHg)	4.1 ± 0.5	3.9 ± 0.6
Heart rate (beats/min)	136 ± 11	147 ± 11
Mean aortic blood pressure (mmHg)	113 ± 8	121 ± 3
Pulmonary artery pressure (mmHg)	14.8 ± 1.0	16.9 ± 1.3
Cardiac output ($ml \cdot min^{-1} \cdot kg^{-1}$)	194 ± 12	179 ± 10
Stroke volume (ml/kg)	1.46 ± 0.06	1.27 ± 0.10
Oxygen consumption ($ml \cdot min^{-1} \cdot kg^{-1}$)	8.06 ± 0.60	8.54 ± 0.47
Blood lactate (mmol/l)	2.10 ± 0.33	2.05 ± 0.41
Base excess (mmol/l)	3.4 ± 0.6	3.2 ± 1.2
Plasma epinephrine (pg/ml)	102 ± 20	258 ± 53*
Plasma norepinephrine (pg/ml)	160 ± 45	279 ± 49†
Plasma renin activity ($ng\ AI \cdot ml^{-1} \cdot h^{-1}$)	9.0 ± 1.6	14.3 ± 4.2
Systemic vascular resistance ($mmHg \cdot l^{-1} \cdot min \cdot kg$)	602 ± 61	678 ± 33
Pulmonary vascular resistance ($mmHg \cdot l^{-1} \cdot min \cdot kg$)	55.1 ± 5.0	75.6 ± 9.0
Mixed venous oxygen tension (mmHg)	45 ± 1	42 ± 1†
Arterial oxygen content (ml/dl blood)	13.1 ± 0.5	13.9 ± 0.8

Values are mean ± SE. n = 10 per group.
* $P < 0.01$, † $P < 0.05$. Absence of symbol indicates difference not statistically significant.

Table 4. Cardiovascular actions of 0.3 MAC halothane in normovolemic swine

	Awake	0.3 MAC
Halothane (end-tidal %)	0.02 ± 0.00	0.37 ± 0.00*
Right atrial pressure (mmHg)	0.6 ± 0.4	0.0 ± 0.8
Pulmonary wedge pressure (mmHg)	1.9 ± 0.3	2.7 ± 0.7
Heart rate (beats/min)	104 ± 9	118 ± 5
Mean aortic blood pressure (mmHg)	132 ± 5	110 ± 6†
Mean pulmonary artery pressure (mmHg)	12.7 ± 1.2	11.4 ± 1.1
Cardiac output ($ml \cdot min^{-1} \cdot kg^{-1}$)	182 ± 10	156 ± 9
Systemic vascular resistance ($mmHg \cdot l^{-1} \cdot min \cdot kg$)	737 ± 64	708 ± 30

Values are mean ± SE. n = 5.
* $P < 0.001$, † $P < 0.01$. Absence of symbol indicates difference not statistically significant.

tration of N_2O, the administration of other drugs or anesthetics, and the existence of heart disease. When sympathetic response is blocked or not possible, depression occurs.[18] Effects of subanesthetic concentrations of N_2O can differ among subjects. Cook *et al.*[28] found "noteworthy variability" of symptoms in volunteers given 20% and 30% N_2O with two of 11 subjects unable to continue testing of reaction time. Eisele and Smith[29] also noted variable central effects of 40% N_2O given to healthy humans; one subject became unconscious when given 30% N_2O. During 30 min of administration of N_2O, these subjects had small decreases in heart rate (6–12%) and cardiac output (11–19%) but relatively larger increases in systemic vascular resistance (18–25%). N_2O has been observed to cause microvascular constriction in rats§ and humans.¶

The increases in plasma norepinephrine levels and heart rate in our hypovolemic swine after administration of 70% N_2O appear to indicate increased sympathetic stimulation. However, the increase in plasma norepinephrine levels could be attributable, in part, to decreased norepinephrine uptake by the lung[30]; and increased heart rate could be a response to the further hypotension. However, arguing against the latter was the fact that swine having the least change in BPa when given N_2O also had the greatest heart rates when given N_2O. Despite sympathetic stimulation, the preponderant response to N_2O in hypovolemic animals was cardiovascular depression. Although the plasma concentrations of vasoactive agents (epinephrine, norepinephrine; and renin activity) increased above awake hypovolemic levels, SVR did not. This vascular response contrasts with the increase in SVR that occurred when N_2O was given to normal humans.[29]

This failure of SVR to increase during hypovolemia despite increases in circulating vasoactive agents implies a direct depressive action of nitrous oxide on the peripheral vasculature. The decreases in mean aortic blood pressure, stroke volume, and cardiac output did not differ from decreases in the same animals given an equipotent dose of halothane, and also imply that N_2O caused myocardial depression. During normovolemia, halothane decreases myocardial contractility[31,32] and has been found by some,[33] but not others,[31] to decrease myocardial compliance. It also inhibits the release and activity of catecholamines.[34,35] In our normovolemic swine, 0.3 MAC halothane decreased mean aortic blood pressure but to a far lesser extent than in the hypovolemic swine. Halothane during normovolemia did not alter other cardiovascular variables, in contrast to its action during hypovolemia.

Despite the pharmacologic differences between the two anesthetics during normovolemia, during hypovolemia the cardiovascular and metabolic effects did not differ. The decreased oxygen consumption and $P\bar{v}_{O_2}$ and increased blood lactate concentration did not differ when animals were given 0.25 MAC N_2O or 0.25 MAC halothane. These results extend previous observations that during hypovolemia, anesthetic actions differ from those during normovolemia.[3–6,8]

These results are analogous to our recent observations[8] that in hypovolemic swine, induction of anesthesia with ketamine also results in cardiovascular depression that does not differ from that produced by thiopental, an agent having no sympathomimetic effects.

All swine in the experiments described here were given an anesthetic. However, in a series of experiments immediately preceding these,[8] we reported that similar awake hypovolemic swine maintained cardiovascular and metabolic stability for a time equal to or greater than that for the current animals. The awake values obtained before and after hemorrhage for the previous animals[8] were also similar to those obtained here using similar methods.

We compared the data for the anesthetized hypovolemic animals reported here with that for the unanesthetized hypovolemic animals reported previously, at similar times after bleeding. We used analysis of variance with repeated measures and the Newman-Keuls method of multiple comparisons.[25] At 5 and 30 min after induction, the two anesthetized groups had lesser SVR, BPa, cardiac output, stroke volume, and $P\bar{v}_{O_2}$, and greater plasma renin activity and blood lactate concentrations than did the unanesthetized swine. The N_2O group had greater norepinephrine concentration and HR than those found in either the halothane group or the unanesthetized group. At 5 min after induction, the two anesthetized groups had greater plasma epinephrine concentration; but at 30 min, no differences in plasma epinephrine concentration existed among groups. Thus, both anesthetics caused deterioration of cardiovascular compensation for hemorrhage.

Since our animals were not "trained," data obtained in the awake, unmedicated, normovolemic state accompanied by endotracheal intubation and mechanical ventilation may not be similar to data obtained for "resting" animals. However, traumatized and/or hypovolemic humans are not in a "resting" state. The cardiovascular data we obtained for the awake, unmedicated normovolemic state fall within the range of values reported by other investigators (see Weiskopf *et al.*[8]). In addition, the few limited reports of hemorrhage in unmedicated swine show an arterial blood pressure response similar to that of our

§ Longnecker DE: Circulatory and microvascular responses to nitrous oxide in the rat. Federation Proceedings 34:771, 1975.

¶ Roth GI, Matheny JL, Gonty AA, O'Reilly JE: Monitoring microvascular reactivity. II. Short-term effect of nitrous-oxide on the peripheral microcirculation in humans. Anesth Prog 27:125–130, 1980.

animals (see Weiskopf *et al.*[8]). Furthermore, 0.3 MAC halothane given to similar awake, normovolemic swine decreased mean aortic blood pressure but had no other cardiovascular effects.

We did not examine the interaction of hemorrhage with other concentrations of these agents because of experimental limitations. At one atmosphere pressure, greater concentrations of N_2O (and consequently of halothane, to ensure comparison of equipotent concentrations) could not have been administered without producing hypoxia in these swine. We did not examine lower concentrations of these agents because we were concerned that an anesthetic concentration of less than 0.25 MAC would result in greater variability of the data. This would have made it more difficult to detect differences (if they existed) between groups and thereby biased the study in favor of our hypothesis.

Our present observations and those previously described[8] support the hypothesis that the sympathetic stimulation caused by some anesthetic agents during normovolemia is not beneficial during hypovolemia. During hypovolemia, N_2O or halothane cause similar deterioration of cardiovascular compensation for hemorrhage at 5 min following administration. Although there is considerable cardiovascular recovery 30 min after induction of anesthesia in the hypovolemic state, the metabolic consequences remain unaltered. Sympathetic stimulation increases oxygen consumption at a time of decreased oxygen supply to tissues. Oxygen transport continues to be inadequate and blood lactate concentration continues to increase. These actions are different from those reported by others for N_2O or halothane during normovolemia and from those we observed for halothane in normovolemic swine. Furthermore, sympathetic stimulation is overwhelmed by the direct depressant actions of the anesthetics, thereby producing cardiovascular depression. Such depression does not differ from that seen with anesthetics with no sympathomimetic properties.

Inasmuch as the use of N_2O during hypovolemia incurs a substantial risk of producing hypoxemia, we cannot support its use during hemorrhage. Furthermore, sympathetic stimulation, whether or not provided by an anesthetic agent, should not be considered a substitute for adequate restoration of blood volume and venous return. Whenever possible, induction of anesthesia should be avoided during hypovolemia; when it cannot be avoided, cardiovascular depression should be expected.

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