Fifty Percent Nitrous Oxide Depresses Recovery from Anoxic Heart Failure Induced by 100% Nitrous Oxide

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In experiments on an isolated rat heart lung preparation, the effects of 100% oxygen, 50% nitrous oxide or air on myocardial metabolism during recovery from anoxic heart failure were evaluated with intramyocardial high energy phosphates, lactate and glycogen. A hundred percent nitrous oxide was administered until the cardiac outpt decreased from 30 to 20 ml/min, and then 50% nitrous oxide, air or 100% oxygen was administered. Fifty percent nitrous oxide reduced the cardiac output and caused heart failure again. The ATP level and energy charge in hearts with 50% nitrous oxide were significantly lower than those in the others. These data indicate that 50% nitrous oxide during recovery from anoxic heart failure had deleterious effects on myocardial function and metabolism. (Key words: anesthetics, gases-nitrous oxide, anoxia-heart failure, heart-metabolism)

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Although an anesthetic machine has been improved to be safer, the administration of pure nitrous oxide by mistake can occur in general anesthesia. It always causes the anoxic heart failure and the subsequent standstill. If it occurs, most anesthesiologists give the heart 100% oxygen immediately to resuscitate it. However, cardiac damage due to oxygen free radicals occurs when reoxygenated[1–3]. Therefore, more reduced oxygen concentrations may be better for the myocardium than 100% oxygen[4,5]. In clinical situations, nitrous oxide or air is only available in order to reduce the oxygen concentration of inspired gas.

Thus, we undertook the present study to investigate the effects of 100% oxygen, 50% nitrous oxide (50% oxygen) or air (21% oxygen) on recovery from the anoxic heart failure induced by 100% nitrous oxide. We selected a rat's heart-lung preparation which was independent of peripheral vascular tone to evaluate the direct effects of these agents on cardiac energy metabolisms during the recovery from the anoxic heart failure.

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Materials and Methods

Male Wistar rats (300–350g) were anesthetized with 50 mg/kg of pentobarbital intraperitoneally. A tracheostomy was performed, and constant volume (1.5ml) intermittent positive pressure ventilation was instituted at a rate of 80 breaths/min with the ambient air. The chest was opened and flooded with icecold saline and the heart was arrested during the preparation. Cannulae were inserted into the aorta and the superior and inferior venae cavae. The cannula of the superior vena cava was used for the monitor of right atrial pressure. A heart

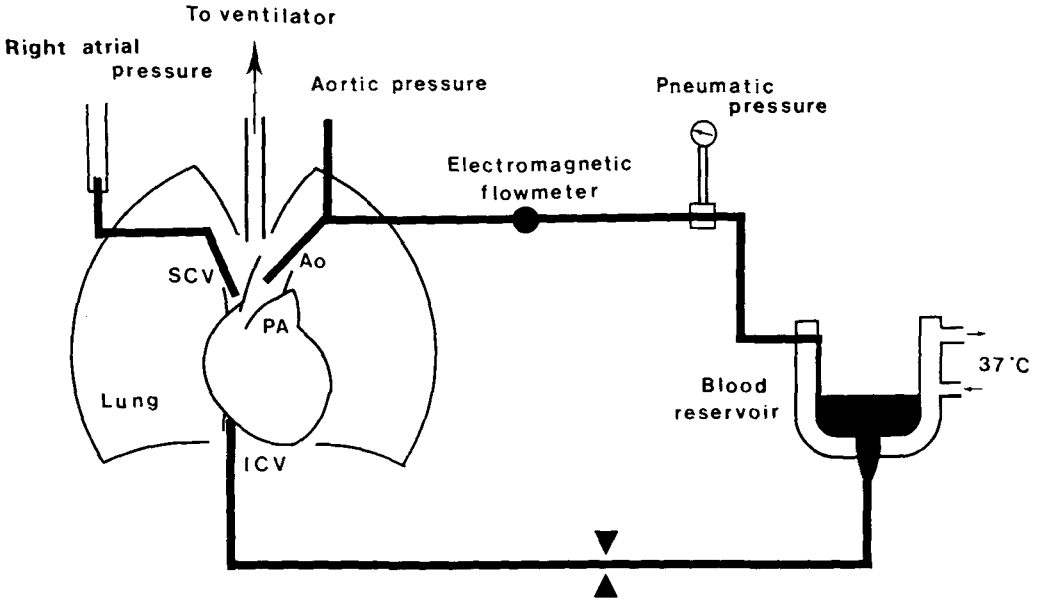

Fig. 1. The schema of heart lung preparation.
Perfusate blood pumped from the aorta was collected in the reservoir, warmed at 37°C and then returned to the inferior vena cava. Abbreviations: Ao; aorta, SCV; superior vena cava, PA; pulmonary artery, ICV: inferior vena cava

lung preparation was perfused with perfusate blood (25 ml), containing red blood cells which were collected from another rat and Krebs Ringer bicarbonate buffer, and its hematocrit and pH were 25 per cent and 7.4 respectively. The concentrations (mM) of the buffer constituents were: NaCl 127, KCl 5.1, $CaCl_2$2.2, KH_2PO_4 1.3, $MgSO_4$ 2.6, $NaHCO_3$ 15, glucose 5.5 and heparin. The perfusate blood pumped from the aorta, passing through a pneumatic resistance, was collected in a reservoir that was warmed at 37°C throughout the experiment by means of a water jacket and then returned to the inferior vena cava. No other organs except heart and lung were perfused (fig. 1). The heart rate was recorded with a Nihonkohden's bioelectric amplifier AB-621G and the cardiac output was measured with a electromagnetic blood flow meter MFV-1200. The arterial pressure and the mean right atrial pressure were measured with carrier amplifiers AP-621G using transducer TP-101T and LPU-0.1A.

All hearts were perfused initially at a cardiac output of 30 ml/min and a mean arterial pressure of 80 mmHg by means of warming with saline and regulating the venous return and the pneumatic resistance. Five minutes after the start of perfusion, 100% nitrous oxide was administered through the lung until the cardiac output decreased from 30 to 20 ml/min. The five hearts were stopped perfusing to obtain the data at this time (group N_{100}). And then 50% nitrous oxide in oxygen (group N_{50}), air (A) and 100% oxygen (O) were administered in groups N_{50}, A and O, respectively (n=8 in each group). Recording of the recovery time started when the cardiac output returned to 30 ml/min.

Either when the cardiac output became zero or 30 min after the start of perfusion, the heart was frozen rapidly between precooled Wollenberger's tongs, and submerged in liquid nitrogen. The other five hearts were also frozen with liquid nitrogen when the cardiac output became 20 ml/min due to 100% nitrous oxide (group N_{100}). Subsequently, the heart tissue

Table 1. The frequency of cardiac failure and recovery time

	N_{50}	A[a]	O[b]
failure	6	0	1
non-failure	2	8	7
recovery time (sec)	62±7	69±14	47±3

a:$P<0.01$, b:$P<0.05$; χ^2-test; When compared with N_{50}. N_{50}: 50% nitrous oxide in oxygen, A:air, O:100% oxygen

was freeze-dried for 6 days. A part of the freeze-dried sample was extracted with perchloric acid and centrifuged at 3000 rpm. High energy phospates (ATP: adenosine triphosphate, ADP: adenosine diphosphate, AMP: adenosine monophosphate and CP: creatine phosphate) and lactate were determined spectrophotometrically by standard techniques according to Bergmeyer[6]. Another piece of freeze-dried sample was placed in 30% KOH and digested in a boiling water bath. Tissue glycogen was extracted, hydrolyzed and assayed as glucose equivalents[7]. The values were expressed as micromoles per gram of dry weight.

Analysis of variance was used for the comparison between the three groups. In comparing with group N_{100}, a non-paired t-test was performed. A χ^2-test was performed to analyze the frequency of heart failure between the three groups. For all tests, a probability of $P<0.05$ was regarded as statistically significant. All values are expressed as means±SEM.

Results

The cardiac output in all groups decreased from 30 to 20 ml/min due to 100% nitrous oxide over 356±30 sec. The mean right atrial pressure in the three groups extremely increased. The blood gas measurements at this time were: pH 7.346±0.006, P_{O_2} 26.9±1.1, P_{CO_2} 14.3±0.2 mmHg (group N_{100}). When 50% nitrous oxide in oxygen, air or 100% oxygen was administered, the cardiac output in all animals except one of group N_{50} returned to previous value. The recovery time were 62±7, 69±14 and 47±3 sec in groups N_{50}, A and

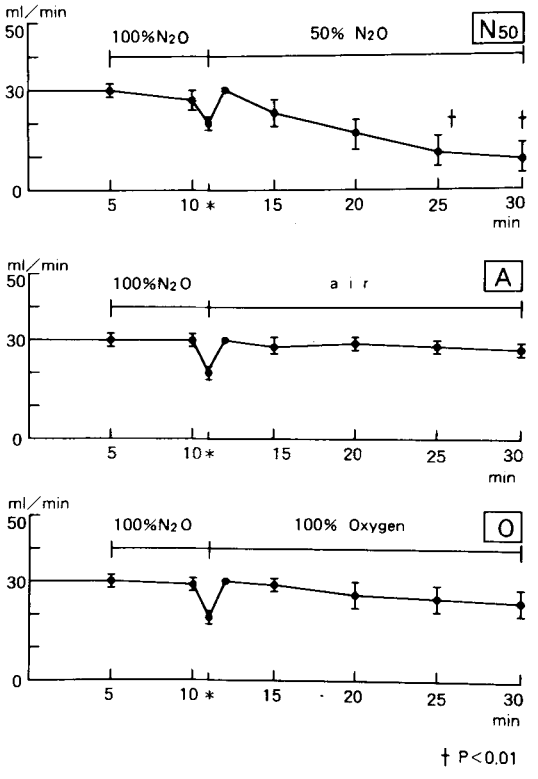

Fig. 2. Changes of cardiac output in three groups. *: at the time of heart failure (cardiac output=20 ml/min)

The cardiac output in all groups decreased from 30 to 20 ml/min due to 100% nitrous oxide over 356±30 sec. The recoveyr time were 62±7, 69±14 and 47±3 sec in groups N_{50}, A and O, respectively. The cardiac output in group N_{50} decreased significantly at 25 and 30 min.

O, respectively. There was no statistically significant difference in the recovery time between the three groups. However, six of eight hearts in group N_{50} and one of eight hearts in group O failed (cardiac output < 20 ml/min) again within 15 min (table 1, fig. 2). The frequency of heart failure in group N_{50} was significantly higher than the others. The blood gas analyses at the end of perfusion are shown in table 2. There were no significant differences in pH and P_{CO_2} between the three groups. The P_{O_2} was different according to the inhaled oxygen concentration. The pH of three groups were lower than that of group N_{100}.

Table 2. Blood gas analyses at the end of perfusion

		pH	Pco_2 (mmHg)	Po_2 (mmHg)
N_{50}	(n=8)	7.194±0.027[a]	15.5±1.2	128.7±6.4
A	(n=8)	7.227±0.025[b]	16.4±0.6	57.2±5.6
O	(n=8)	7.206±0.034[a]	16.14±0.9	205.2±18.5
N_{100}	(n=5)	7.346±0.006	14.3±0.2	26.9±1.1

a:$P<0.005$, b:$P<0.01$; When compared with the values in group N_{100}. (non-paired t test)
N_{50}: 50% nitrous oxide in oxygen, A: air, O: 100% oxygen
N_{100}: 100% nitrous oxide

Table 3. Systolic blood pressure, heart rate and mean right atrial pressure

Time	5	10	*	15	20	25	30
SBP (mmHg)							
N_{50}	88±2	96±2	90±2	96±3 (n=7)	84±5 (n=7)	91±3 (n=4)	92±1 (n=3)
A	86±6	99±2	86±3	98±2	97±1	93±1	92±1
O	90±2	99±2	87±3	94±1	92±1 (n=7)	90±1 (n=7)	90±1 (n=7)
HR (beats/min)							
N_{50}	235±11	254±10	251±9	248±6 (n=7)	219±22 (n=7)	244±11 (n=4)	243±23 (n=3)
A	242±10	244±9	242±11	245±10	234±9	233±10	219±10
O	246±7	262±12	245±11	243±8	238±9 (n=7)	223±8 (n=7)	220±8 (n=7)
RAP (kPa)							
N_{50}	0.29±0.01	0.35±0.04	1.11±0.05	0.58±0.16 (n=7)	0.91±0.33 (n=7)	0.77±0.40 (n=4)	0.78±0.10[a] (n=3)
A	0.28±0.02	0.33±0.03	1.05±0.07	0.48±0.13	0.33±0.03	0.31±0.02	0.31±0.02
O	0.28±0.02	0.36±0.05	0.95±0.19	0.36±0.10	0.27±0.03 (n=7)	0.29±0.04 (n=7)	0.31±0.05 (n=7)

SBP: systolic blood pressure, HR: heart rate, RAP: mean right atrial pressure.
a: $P<0.01$; Analysis of variance between 3 groups
*: The time when the cardiac output decreased to 20 ml/min. (10'56"±30")
N_{50}: 50% nitrous oxide in oxygen, A: air, O: 100% oxygen

There were no significant differences in the systolic blood pressure and heart rate between the three groups without the data in failed hearts. However, the mean right atrial pressure in group N_{50} was higher than that of the others at the end of perfusion (table 3).

In cardiac metabolites, there were no significant differences in ADP, AMP, CP, lactate and glycogen between the three groups. But ATP level and energy charge (EC: [ATP+0.5×ADP]/[ATP+ADP+AMP]) in group N_{50} were significantly lower than those in the other groups. When compared with group N_{100}, ATP levels and EC in groups A and O, and CP levels in the three groups were higher than those in group N_{100}. ADP levels in groups A and O and AMP level in group O were lower than those in group N_{100} (table 4).

Discussion

The oxygen concentrations did not affect the recovery from the anoxic heart failure induced by 100% nitrous oxide, because there were no significant differences in the

Table 4. Cardiac metabolites (All values except EC are expressed as micromoles per gram of dry weight)

	ATP	ADP	AMP	CP	EC	Lactate	Glycogen
N_{50}	14.79±1.03*	3.25±0.34	0.771±0.269	16.59±0.48[a]	0.868±0.017**	35.5±3.7	60.9±5.6
A	18.00±0.72[b]	2.45±0.18[b]	0.558±0.077	22.57±2.60[b]	0.917±0.007[a]	32.6±2.2	67.5±4.0
O	18.14±0.43[b]	2.76±0.42[c]	0.498±0.076[c]	21.25±1.34[a]	0.913±0.012[b]	30.3±2.4[c]	82.5±8.0
N_{100}	14.37±0.47	4.11±0.26	0.801±0.103	9.11±0.72	0.852±0.004	38.4±2.3	69.4±5.7

*: $P<0.01$, **: $P<0.05$; Analysis of variance between 3 groups.
a: $P<0.001$, b: $P<0.005$, c: $P<0.05$; When compared with the values in group N_{100}. (non-paired t test)
N_{50}: 50% nitrous oxide in oxygen, A: air, O: 100% oxygen, N_{100}: 100% nitrous oxide

cardiac function and metabolisms between groups A and O. However, fifty per cent nitrous oxide caused the heart failure more frequently during the recovery from the anoxic heart failure than air or oxygen did. This may have been due to direct myocardial depressant effects of nitrous oxide. Although Goldberg et al.[8] reported that nitrous oxide did not possess any direct myocardial depressant or stimulatory properties, Price[9] indicated the myocardial depression by nitrous oxide in cat's papillary muscle. There are many reports that indicate the myocardial depression by nitrous oxide in clinical studies[10–13]. Eisele et al.[14] demonstrated that myocardial depression occurred in patients with impaired left ventricular function. This finding may be consistent with our results that 50% nitrous oxide depressed the heart with impaired function by anoxia. More recently, similar depressant effects of nitrous oxide have been shown by Weiskopf and Bogetz[15] in hypovolemic swine.

Nitrous oxide also has mild sympathomimetic properties[16,17]. Because our preparation was independent of central nervous system and free from peripheral vascular tone, nitrous oxide did not show the sympathomimetic effect in this experiment. Therefore, it is likely that 50% nitrous oxide might cause the heart failure due to the direct myocardial depressant effects.

In cardiac energy metbolisms, the levels of CP in the three groups increased from the level at the time of heart failure induced by 100% nitrous oxide (group N_{100}). However, ATP level and EC in group N_{50} were significantly lower than those in the other two groups. The values were close to those in group N_{100}. The levels of ADP in groups A and O, AMP and lactate in group O significantly dereased when compared with those in group N_{100}. We can say from these results that the administration of 50% nitrous oxide did not improve the metabolic dysfunction induced by anoxia or caused the metabolic dysfunction again. The latter may acount for the results. The metabolic dysfunction in group N_{50} seems to have resulted from the frequency of heart failure, because the levels of ATP in two non-failed hearts of group N_{50} were above 18 micromoles per gram of dry weight. We consider that nitrous oxide itself did not affect directly the cardiac energy metabolisms. The direct myocardial depressant effects of nitrous oxide might cause the cardiac pump failure and result in the metabolic deterioration. Therefore, it is unlikely that the myocardial metabolic change by nitrous oxide might cause the heart failure.

The blood pH in the three groups were significantly lower than that in group N_{100}. The perfusate blood seems to have become acidic at the end of reperfusion because of the anoxia. The blood P_{CO_2} in all groups were low because the heart were the only organ that produced carbon dioxide in this preparation. The P_{O_2} was different according to the fraction of inhaled oxygen. The differences of oxygen tension did not correlate with the frequency of heart failure during the recovery. The influence of nitrous oxide seems to have exceeded that of oxygen concentrations. However, it is interesting that one of hearts in group O failed again

during the recovery. This may be due to oxygen free radicals. Further studies need to be done about their effects on the reoxygenated heart.

Although these results from the animal study cannot be transferred directly to humans, an attention should be paid when nitrous oxide is administered to the heart with impaired function by anoxic stress.

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