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Nitrous oxide does not depress left ventricular contractility in ischemic rat heart

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Abstract: The direct effects of nitrous oxide on left ventricular contractility and myocardial oxygen consumption (MVO_2) in the ischemic isolated rat heart were studied. The rat heart was isolated and perfused by a Langendorf technique. The aortic stump was cannulated and the heart was perfused with Kumpeis solution bubbled with 95% O_2 and 5% CO_2 (control phase). A latex balloon was inserted into the left ventricle (LV) to measure LV pressures and d*P*/d*t*. Coronary flow was measured and MVO_2 was calculated. After the control phase, perfusion pressure was decreased to induce global ischemia (ischemic phase). There were four groups of eight hearts each: control, nitrogen, nitrous oxide, and halothane groups. After 15 min of ischemic phase, the perfusion pressure was increased and the gas mixture was changed to the standard gas mixture (reperfusion phase). Nitrous oxide did not further depress myocardial contractility compared with nitrogen in the ischemic phase, and did not alter MVO_2 in the ischemic phase compared with nitrogen. Halothane significantly depressed myocardial contractility and decreased MVO_2 in the ischemic phase compared with the control.

Key words: Nitrous oxide, Myocardial ischemia, Halothane, Isolated heart, Myocardial oxygen consumption

Introduction

Nitrous oxide has been widely used to anesthetize patients with coronary artery disease, and it is also used to obtain pain relief in patients with acute myocardial ischemia [1]. Although a number of studies have been attempted to determine the effects of nitrous oxide on myocardial function, the data are still conflicting. There have been several reports which showed deleterious effects of nitrous oxide on ischemic myocardium [2–5]; however, in most of these studies, nitrous oxide was used in conjunction with other potent inhalation agents or narcotics. Anesthetic agents can have significant effects on systemic and pulmonary circulation. To demonstrate the effects of nitrous oxide on ischemic myocardium, both preload and afterload must be controlled.

We designed this study to demonstrate the direct effect of nitrous oxide on ischemic myocardium. We used an isolated perfused working rat heart model to control preload, afterload, and heart rate.

Materials and methods

Male Lewis rats weighing 250–300 g were used. Pentobarbital 65 mg/kg and heparin 1000 units/kg were injected intraperitoneally. After the rat was anesthetized, the heart was excised through a bilateral thoracotomy and pericardiotomy and immediately placed in cold saline. After contractions ceased, the aortic root was cannulated with a 16-gauge cannula, and the heart was perfused in a retrograde fashion using a modified Langendorf apparatus (Fig. 1). This procedure took less than 3 min after excision. The perfusate consisted of Kumpeis solution which contained KH_2PO_4 1.2 mM/l, KCL 4,7 mM/l, $CaCl_2$-H_2O 1.75 mM/l, NaCl 109 mM/l, Na pyruvate 11 mM, Na_2 EDTA 0.5 mM/l, $NaHCO_3$ 25 mM/l, $MgSO_4$ 1.2 mM, and glucose 11 mM/l. The pH of the solution was adjusted to 7.4 with $NaHCO_3$. The perfusate was bubbled with 95% O_2 and 5% CO_2 to achieve Po_2 greater than 480 mmHg and Pco_2 of about 40 mmHg. The initial coronary inflow pressure was set at 80 mmHg. After perfusion was started, a latex balloon was inserted into the left ventricle (LV) through the left atrium and mitral valve to control preload by a certain balloon volume, and to measure intraventricular pressure and d*P*/d*t*. Pacemaker wires were sewn to the right ventricle to pace the

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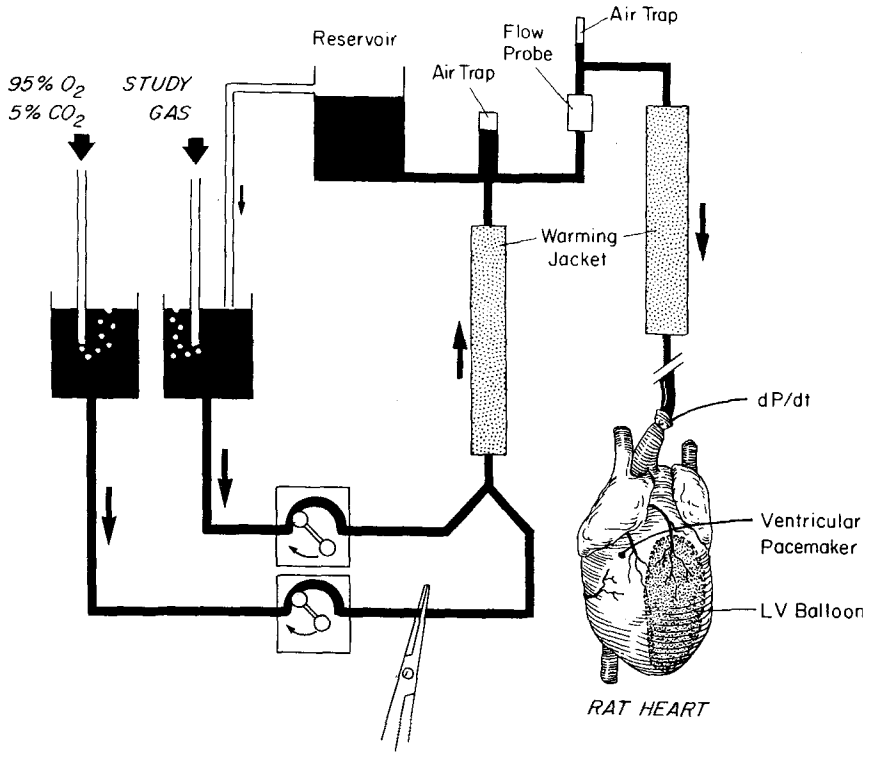

Fig. 1. Diagram of the Langendorf apparatus. Two different gas mixtures were bubbled in the separate reservoirs. The perfusate bubbled with the different gas mixture was switched by clamping the circuit. LV, left ventricular

heart at a rate of 250 beats/min. The isolated heart was submerged in the perfusate in the test tube at a constant temperature of 37°C.

Normal saline was added the LV balloon to obtain LV systolic pressure above 100 mmHg. If a left ventricular end-diastolic pressure (LVEDP) greater than 10 mmHg was required to achieve LV systolic pressure greater than 100 mmHg, the heart was discarded.

The following measurements were performed: LVEDP, left ventricular systolic pressure (LVSP), left ventricular developed pressure [LVDP (LVSP minus LVEDP)]. The perfusate from the right ventricle and atrium (i.e., coronary flow) was drained into the test tube. The perfusate samples were withdrawn from the aortic cannula (inlet) and the perfusate in the test tube (i.e., coronary flow drain) to measure gas pressures. Myocardial oxygen consumption (MVO_2) was calculated as follows: $MVO_2 = (PiO_2\text{-}PoO_2)x\ K\ x$ coronary flow [K, solubility coefficient; PiO_2, oxygen partial pressure in the inflow sample; PoO_2, oxygen partial pressure in the outflow sample].

The rat heart was initially perfused at a pressure of 80 mmHg for 15 min (control phase). Hemodynamic and metabolic parameters were measured. After this stabilization period, global ischemia was induced by decreasing the perfusion pressure to 40 mmHg (ischemic phase). The gas mixture was changed from the standard mixture (95% O_2 and 5% CO_2) to the gas mixtures given in the schedule (Table 1). The hearts were divided into five groups of eight hearts each. Group 1 received 95% O_2 and 5% CO_2, and served as a control group. Group 2 received 50% introgen, 45% O_2, and 5% CO_2 (nitrogen group). Group 3 received 50% nitrous oxide, 45% O_2, and 5% CO_2 (nitrous oxide group). Group 4 received 95% O_2, 5% CO_2, and 0.4% halothane (halothane group). In the control and halothane groups, PiO_2 was greater than 450 mmHg. In

Table 1. Study protocol gas mixtures

Group	Control phase (20 min)	Ischemic phase (15 min)	Reperfusion phase (15 min)
Control	$O_2 : CO_2 = 95 : 5$	$O_2 : CO_2 = 95 : 5$	$O_2 : CO_2 = 95 : 5$
Nitrogen	$O_2 : CO_2 = 95 : 5$	$O_2 : CO_2 : N_2 = 45 : 5 : 50$	$O_2 : CO_2 = 95 : 5$
Nitrous oxide	$O_2 : CO_2 = 95 : 5$	$O_2 : CO_2 : N_2O = 45 : 5 : 50$	$O_2 : CO_2 = 95 : 5$
Halothane	$O_2 : CO_2 = 95 : 5$	$O_2 : CO_2 : Hal = 95 : 5 : 0.4$	$O_2 : CO_2 = 95 : 5$

All values are per cent.
Hal, halothane.

the nitrous oxide and nitrogen groups, PiO_2 ranged from 260 to 350 mmHg. In each group, $PiCO_2$ ranged between 34 mmHg and 47 mmHg with pH ranging between 7.30 and 7.46. After 10 min of global ischemia, the aforementioned hemodynamic and metabolic parameters were measured.

After 15 min of the ischemic phase, the perfusion pressure was raised from 40 mmHg to 80 mmHg (reperfusion phase), and the gas mixture was changed to the standard gas mixture in all groups. After 15 min of stabilization, the hemodynamic parameters and gases in the perfusate were measured. The study was terminated after these measurement, and the LV was weighed and sectioned to determine if there were gross areas of infarction.

Data were analyzed by Student's *t*-test and analysis of variance. A *P* value of less than 0.05 was considered to be significant.

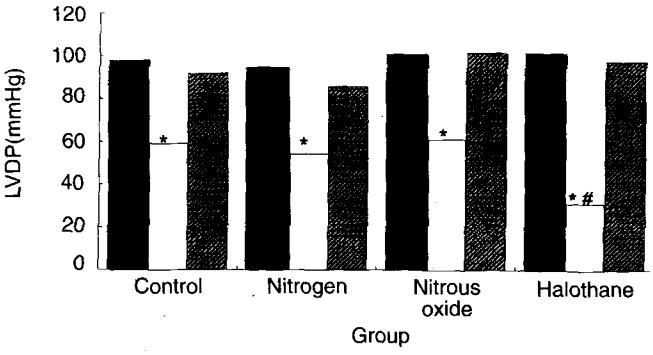

Fig. 2. Left ventricular developed pressure (*LVDP*) in the ischemic phase was significantly lower than that in the control phase in all groups ($P < 0.01$). LVDP in the ischemic phase in halothane group was significantly lower than that in the other groups. Control, *solid bars*; ischemia, *open bars*; reperfusion, *hatched bars*

Results

Hemodynamic data (Table 2, Fig. 2)

There were no significant differences in hemodynamic data (i.e., LVEDP, LVDP, and d*P*/d*t*) among all the groups in the control phase. In the ischemic phase, LVSP and LVDP were significantly lower in all groups compared with the control phase ($P < 0.01$).

In the ischemic phase, the LVSP, LVDP, and LV d*P*/d*t* were significantly lower in the halothane group than those in the other groups ($P < 0.01$). In the reperfusion phase, the LVSP, LVDP, and LV d*P*/d*t* were lower in all groups compared with in the control phase. However, these changes were not significant.

Table 2. Hemodynamic data

Group	Phase	Left ventricular systolic pressure (mmHg)	Left ventricular d*P*/d*t*
Control	Control	105 ± 8	1770 ± 102
	Ischemia	64 ± 8*	1217 ± 103*
	Reperfusion	98 ± 7	1730 ± 278
Nitrogen	Control	101 ± 6	1706 ± 132
	Ischemia	59 ± 7*	1223 ± 131*
	Reperfusion	94 ± 2	1585 ± 183
Nitrous oxide	Control	107 ± 8	1686 ± 139
	Ischemia	57 ± 7*	1329 ± 250*
	Reperfusion	106 ± 10	1721 ± 212
Halothane	Control	107 ± 4	1660 ± 87
	Ischemia	37 ± 13*#	605 ± 296*#
	Reperfusion	104 ± 7	1578 ± 153

Data are mean ± S.E.M.
* $P < 0.01$ compared with the control value in the group.
# $P < 0.01$ compared with the other groups.

MVO_2 (Table 3)

There were no significant differences in MVO_2 in the control phase among all groups. Myocardial oxygen consumption in the ischemic phase was significantly lower than the control phase in all groups. MVO_2 in the halothane group was significantly lower than in the other groups ($P < 0.01$).

Coronary flow (Table 3)

The coronary flow was significantly decreased in the ischemic phase in all groups; however, there were no significant intergroup differences.

Table 3. Coronary flow and myocardial oxygen consumption (MVO_2)

Group	Phase	Coronary flow (ml/min)	MVO_2 (mMol/g/min)
Control	Control	23.6 ± 2.9	4.8 ± 0.3
	Ischemia	14.4 ± 6.1*	2.5 ± 0.2*
	Reperfusion	25.1 ± 3.3	4.7 ± 0.2
Nitrogen	Control	21.3 ± 2.3	5.0 ± 0.2
	Ischemia	8.9 ± 1.6*	5.0 ± 0.2*
	Reperfusion	20.7 ± 4.1	2.0 ± 0.2
Nitrous oxide	Control	20.7 ± 4.1	4.3 ± 0.3
	Ischemia	13.0 ± 5.3*	2.0 ± 0.3*
	Reperfusion	21.8 ± 1.8	4.5 ± 0.2
Halothane	Control	21.0 ± 2.2	4.8 ± 0.3
	Ischemia	10.6 ± 2.5*	1.5 ± 0.2*#
	Reperfusion	21.3 ± 3.2	4.3 ± 0.2

Data are mean ± S.E.M.
* $P < 0.01$ compared with control values within the group.
# $P < 0.01$ compared with control group.
MVO_2, myocardial oxygen consumption.

Myocardial infarction

No gross area of infarction was seen in any of the studied hearts.

Discussion

We found that 50% nitrous oxide did not further depress LV function in globally ischemic isolated rat hearts during isovolumic contractions.

The effect of nitrous oxide on myocardial function are not well-defined although a number of studies have been performed, some suggesting a cardiac depressant effect [6,7], others a cardiac stimulant effect [8–10], and still others no effect on myocardial contractility [11,12]. The explanation for the conflicting data may be that the effects of nitrous oxide are dependent on several factors such as experimental model (animal or human, in vivo or in vitro), the presence of the heart disease, the concentration of nitrous oxide, anesthetic effect on systemic organs such as adrenal glands, and in the concomitant use of other anesthetic agents. We used the isolated rat heart perfused by a Langendorf apparatus to control the intraventricular balloon volume (preload), coronary inflow pressure, and heart rate with pacing. This eliminated the effects of nitrous oxide on pulmonary circulation. Thus, we were able to demonstrate the direct effects of nitrous oxide on myocardial contractility.

Most of the studies which suggested a cardiac depressant effects for nitrous oxide used it in conjunction with other anesthetic agents which affect cardiovascular function. Even in the studies in which nitrous oxide alone was used, its effects on systemic and pulmonary circulation could not be excluded in the in vivo model. Eisele et al. [7] showed an increase in systemic vascular resistance, an increase in plasma norepinephrine levels, a decrease in heart rate, and a decrease in cardiac output using 40% nitrous oxide in healthy volunteers; however, the decrease in cardiac output was related to a decreased heart rate and increased systemic vascular resistance and was not necessarily due to a direct cardiac depressant effect. The direct effect of nitrous oxide on myocardial function is not clear. Eisele et al. [7] also showed that the cardiac depressant effects of nitrous oxide were seen only in patients with coronary artery disease and poor LV function (ejection fraction less than 0.50 and/or ventricular dyskinesis) during cardiac catheterization. However, they failed to show the cardiac depressant effect of nitrous oxide in patients without cardiac disease under similar conditions. Nathan [5] demonstrated that nitrous oxide aggravated myocardial ischemia when administered in conjunction with isoflurane in dogs. The effects of isoflurane on myocardial ischemia and coronary circulation remains controversial. Reiz [3] demonstrated that nitrous oxide augmented the systemic and coronary hemodynamic effects of isoflurane. Mitchell et al. demonstrated that nitrous oxide did not induce myocardial ischemia in patients with ischemic heart disease and poor ventricular function, and who were anesthetized with fentanyl [13]. Cahalan et al. also failed to demonstrate that nitrous oxide induced wall motion abnormalities indicative of myocardial ischemia in patients with ischemic heart disease anesthetized with fentanyl [14]. The effects of nitrous oxide itself on myocardial ischemia cannot be defined.

Kawamura et al. [8] showed that nitrous oxide has positive inotropic effects. The cardiostimulatory effects might be attributed to light anesthesia, hypercapnia, or increased serum levels of catecholamines. In our model, these factors were excluded.

Some human studies suggested that nitrous oxide did not depress myocardial function in patients with cardiac disease. Goldberg et al. reported that nitrous oxide had no effect on isolated rat LV trabeculae carneae muscle contractility [15]. Our data support that. The extent of decrease in MVO_2 in the ischemic phase in the nitrous oxide group was similar to that in the nitrogen group. We therefore believe that nitrous oxide does not change myocardial metabolism in the ischemic heart.

We confirmed the cardiac depressant effects of halothane [16,17]. In our study, a relatively low concentration of halothane markedly depressed LV function and decreased MVO_2 in the globally ischemic rat heart. The complete recovery observed after ischemic insult in the halothane group suggests that a favorable myocardial oxygen supply/demand ratio was maintained during the ischemic phase. However, it must be interpreted with caution because coronary inflow pressure was kept constant at 40 mmHg despite a marked fall in LVSP.

In conclusion, 50% of nitrous oxide did not further depress myocardial function or change MVO_2 in globally ischemic contracting rat hearts.

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