Nitrous Oxide added to Halothane Reduces Coronary Flow and Myocardial Oxygen Consumption in Patients with Coronary Disease

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The haemodynamic and myocardial metabolic effects of adding 50 per cent nitrous oxide to 0.5 per cent halothane were studied in 13 patients, before the surgical incision for coronary artery vein grafts. Cardiac output and coronary sinus blood flow were determined by thermodilution, along with haemodynamic measurements. Measurements 15 minutes after addition of nitrous oxide revealed a significant decrease in heart rate, arterial pressure, cardiac index, coronary sinus blood flow and myocardial oxygen consumption. There was a significant increase in coronary sinus lactate content, and a significant decrease, from 27 to 11 per cent, in myocardial lactate extraction. We conclude that these circulatory changes were likely to be due to a depression of ventricular function by the nitrous oxide. The myocardia of these patients with severe coronary disease were becoming globally ischaemic while they were receiving 50 per cent oxygen, in the presence of hypotension. Nitrous oxide should be turned off when hypotension occurs in coronary patients.

Key Words

HEART: coronary disease, myocardial function, anaesthetics. ANAESTHETICS, GASES: nitrous oxide, BLOOD PRESSURE: drug effects.

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Until a decade or so ago, nitrous oxide (N_2O) was considered to have no appreciable circulatory effects, providing hypoxia was not present. In 1970 Smith and co-workers¹ found in healthy volunteers that adding 70 per cent N_2O to stable concentrations of halothane caused elevated systemic vascular resistance and arterial pressure, but no change in cardiac output. Then Eisele and Smith² reported in healthy man, that 40 per cent N_2O depressed myocardial function, but increased systemic resistance, which maintained arterial pressure. In 1980, Wynne *et al.*³ assessed the effects of 50 per cent N_2O on left ventricular function in patients with coronary disease. They found a small decrease in heart rate and cardiac index and no change in blood pressure. In patients with coronary disease, addition of N_2O to both morphine⁴ and fentanyl⁵ depresses left ventricular function, with reduced blood pressure, stroke work and cardiac output. Given with fentanyl, 60 per cent N_2O also slowed the heart rate.⁵

Hence we studied the effects of adding 50 per cent N_2O to 0.5 per cent halothane in oxygen, in 13 patients anaesthetized for coronary artery bypass grafting (CABG). Cardiac function and haemodynamics were studied plus myocardial energy metabolism, including coronary sinus blood flow (CBF), myocardial oxygen consumption (MVO_2) and lactate extraction as indicators of oxygen balance.

This investigation was part of a larger study of 30 patients which extended from before induction of anaesthesia, through operation for CABG and for

24 hours postoperatively.⁶ All protocols were approved by the Human Subjects Committee of Cedars-Sinai Medical Center. Signed informed consent was obtained. All 13 patients had serious coronary disease, but none had depressed ventricular function (all ejection fractions above 0.5). Their mean age was 58.6 years and mean weight was 79 kg. Their functional status by New York Heart Association was: Class II – 7, III – 4, IV – 2. Six patients were taking propranolol and nine had previous myocardial infarction. They subsequently received a mean of 3.8 vein grafts. None of the patients had a perioperative infarction.

Methods

The N₂O study was done after endotracheal intubation but before the surgical incision was made. Before induction of anaesthesia, after secobarbital premedication (mean dose: 210 mg) and lidocaine infiltration, a radial artery cannula was inserted, plus two thermofluid catheters, both via the right internal jugular vein. In addition to the usual pulmonary arterial catheter⁷ (Edwards Co.) another special preshaped eight Fr thermistor-equipped catheter (Wilton-Webster Labs) was placed in the midcoronary sinus, aided by fluoroscopy. The latter catheter⁸ measures total coronary sinus blood flow which represents virtually all of left coronary arterial flow.

Induction of anaesthesia in these 13 patients had been initiated with a small dose of thiopental (mean = 133 mg) followed by halothane-oxygen for a mean of 14.6 minutes before intubation. After intubation, when circulatory dynamics had returned to levels present when awake (mean arterial pressure 95 mmHg, mean cardiac index 2.59 L/min/m²) and with 0.5 per cent halothane being given, control measurements were done. At a mean of 14.2 minutes after intubation, 50 per cent N₂O was added to the inspired mixture with controlled ventilation. The second series of measurements was after 15 minutes of N₂O administration.

Each series consisted of measuring cardiac output (duplicate), total CBF, arterial and central pressures and sampling arterial and coronary sinus blood for hemoglobin, oxygen and lactate contents. Haemodynamic indices were calculated using standard formulas.⁹ Hemoglobin and oxygen saturation was determined by co-oximetry (IL Co-oximeter, Model 282) and oxygen content calculated as: $Hb \times O_2 \text{ per cent saturation} \times 1.34$, for ml O₂/100

ml of blood. MVO₂ in ml/minute was calculated as: $CBF \text{ (ml/min)} \times \text{ART-CS difference of content of oxygen, in ml/100 ml}$. Lactate measurement was by a modification of the Marbach method.¹⁰ The myocardial lactate extraction ratio was calculated from the formula $\text{ART-CS/Art.} \times 100$, where ART and CS are the concentrations of lactate in mmol/L, in arterial and coronary sinus blood.

The Wilcoxon paired rank test was employed for statistical evaluations.

Results

With constant mechanical ventilation, before and during N₂O administration, mean PaCO₂ was 39 ± 5 and 35 ± 6 mmHg and mean pH was 7.42 ± 0.06 and 7.46 ± 0.06. Mean PaO₂ on 50 per cent N₂O was 170 ± 41 mmHg compared to 350 ± 60 before it. The mean bicarbonate concentration, at 25 ± 1.9, did not change.

TABLE I: After 15 minutes of N₂O, there were highly significant decreases in heart rate, mean arterial pressure and hence rate-pressure product. Cardiac index also fell 18 per cent ($p < 0.003$), without change in stroke volume. The 35 per cent reduction ($p < 0.003$) in mean stroke work was due to the fall in blood pressure. While right atrial pressure was unchanged and pulmonary capillary wedge pressure showed a statistically non-significant decrease, mean pulmonary arterial pressure did decrease significantly ($p < 0.01$). Pulmonary vascular resistance was unchanged but systemic vascular resistance was reduced significantly ($p < 0.01$).

TABLE II: Mean total CBF had a highly significant decrease from 96 to 61 ml/minute ($p < 0.002$). Along with the small but statistically significant decrease in oxygen content of coronary sinus blood, this produced a 35 per cent reduction in calculated MVO₂ ($p < 0.002$). With no alteration in lactate content of arterial blood, a 19 per cent increase occurred in lactate content of coronary sinus blood ($p < 0.04$). This was reflected by a change from 27 to 11 per cent in mean lactate extraction by the ventricular muscle.

A reduction in lactate extraction occurred in nine of the 13 patients. In two patients, changes from 32 and three per cent extraction, to 52 and 62 per cent lactate production, respectively, occurred as CBF fell 44 and 49 per cent in each. No alteration in ST segment configuration was seen during administration of the N₂O.

TABLE I Haemodynamic Data

	Control	On 50% N ₂ O	p Value
Rate beats/minute	72 ± 13*	64 ± 9	<0.003
Mean arterial pressure mmHg	101 ± 16	74 ± 15	<0.002
Rate-pressure product	10,373 ± 2484	6650 ± 1694	<0.002
Cardiac index L/minute/M ²	2.48 ± 0.5	2.03 ± 0.4	<0.003
Stroke volume index ml/beat/M ²	34.9 ± 7	32.1 ± 5	N.S.
Stroke work index GmM/M ²	54 ± 10	35 ± 10	<0.003
Right atrial pressure mmHg	8 ± 4	8 ± 3	N.S.
Mean pulmonary arterial pressure mmHg	18 ± 4	15 ± 3	<0.01
Pulmonary capillary wedge pressure mmHg	16 ± 5	13 ± 3	N.S.
Systemic vascular resistance Dynes · Sec · Cm ⁻⁵	1671 ± 552	1412 ± 481	<0.01
Pulmonary vascular resistance Dynes · Sec · Cm ⁻⁵	318 ± 119	326 ± 74	N.S.

n = 13. *Mean ± S.D. N.S. – Not Significant.

TABLE II Myocardial Blood Flow and Metabolism

	Control	On 50% N ₂ O	p Value
Coronary blood flow ml/minute	96 ± 32*	61 ± 18	<0.002
Coronary sinus O ₂ content ml/100 ml	7.0 ± 1.2	6.5 ± 1.3	<0.02
Myocardial VO ₂ ml/minute	8.2 ± 3.3	5.3 ± 1.9	<0.002
Arterial lactate mmol/L	1.20 ± 0.37	1.18 ± 0.42	N.S.
Coronary sinus lactate mmol/L	0.85 ± 0.21	1.01 ± 0.37	<0.01
Myocardial lactate extraction %	27 ± 13	11 ± 32	<0.04

n = 13. *Mean ± S.D. N.S. – Not Significant.

Discussion

The cardiovascular effects of N₂O depend on several factors, including the model studied (animal or human), presence of coronary disease, when one looks for effects, how much N₂O is given and importantly, whether other agents are also given. In the dog, Thorburne *et al.*¹¹ report that with 65–70 per cent N₂O for 15 minutes, cardiac output decreased, but systemic resistance and atrial pressure increased. Heart rate, arterial pressure, coronary blood flow and resistance and MVO₂ were unchanged. In patients with coronary disease, 50 per cent N₂O given alone did not produce important depression of ventricular performance but evidence of a decline in MVO₂ was seen.³ In healthy man, 40 per cent N₂O decreased heart rate and cardiac output but raised systemic resistance with no change in blood pressure.² These investigators also documented a rise in plasma norepinephrine in the first 15 minutes of N₂O. Adding 70 per cent N₂O to steady state halothane anaesthesia in healthy man

has given another set of responses: no depression of cardiac output, elevation of vascular resistance, arterial and right atrial pressures.¹ These investigators concluded their effects to be from sympathetic stimulation and not to a change in oxygen concentration. They also pointed out that their N₂O studies were done after the initial circulatory adaptation to halothane had occurred.¹²

Maintenance of anaesthesia with halothane and nitrous oxide is common in patients having CABG. In the period after endotracheal intubation but before the autonomic stimulation of the surgical incision, a fall in blood pressure can occur. We have been concerned whether, during hypotension in such patients, there is a risk of inadequate myocardial oxygenation, or even severe ischaemia and infarction. So we investigated that combination: N₂O (50 per cent) and a small concentration of halothane (0.5 per cent) given at that time, to determine their effects, unassociated with effects of the operation. Fifteen minutes was chosen as the

time for full effect of N_2O . Compared to the 2–3 per cent halothane that had been given for at least 15 minutes during induction of anaesthesia, 0.5 per cent inspired halothane along with N_2O , should have produced a lower end-tidal concentration with a diminished halothane effect on the circulation. Unfortunately we did not determine end-tidal concentrations.

We found a 27 per cent reduction in blood pressure, due to decreases in cardiac index (18 per cent), heart rate (11 per cent) and systemic resistance (15 per cent). The latter decreased in 10 of the 13 patients. Normally this reduction in afterload would be expected to increase stroke volume and cardiac index. However, in our patients, stroke volume did not change. One possible explanation for this, which we saw in our study of nitroglycerine¹³ in these same patients, is that the decrease in afterload is accompanied by a similar decrease in preload (capillary wedge pressure), which offsets the expected increase in stroke volume. Since wedge pressure did not change significantly with N_2O , we cannot invoke that explanation.

Another explanation for the failure of stroke volume to increase with afterload reduction, during N_2O , is a direct myocardial depressing effect, i.e. a reduction in contractility, as others have concluded.^{4,5} Figure 1 plots mean stroke work index against mean capillary wedge pressure, plus the individual responses to N_2O in all 13 patients. The 35 per cent reduction in stroke work with no significant change in mean wedge pressure suggests a shift in the cardiac function curve to one of more depressed function.

Cardiac index fell in our patients mainly because of a slower heart rate, since stroke volume did not change. Thus the systemic haemodynamics suggest a depression of both myocardial inotropic and chronotropic functions.

The reduction in coronary blood flow was likely secondary to a decrease in coronary perfusing pressure (arterial pressure). This may be interpreted in two ways. Firstly, one may say that the myocardium is depressed and does not need as large a coronary flow, i.e. myocardial metabolic needs are decreased. If this were true, there should be a reduced myocardial oxygen extraction, with a consequent increase in oxygen content of coronary sinus blood. That is, the heart worked 35 per cent less, consumed 35 per cent less oxygen (MVO_2) and coronary flow decreased 35 per cent. However,

FIGURE 1 The mean capillary wedge pressure is plotted against mean stroke work index for 13 patients, before and during N_2O . In addition, the individual patient responses to N_2O are shown. Mean stroke work decreased 35 per cent without real change in wedge pressure, suggesting a change to more depressed ventricular function.

that was not the case and another explanation is necessary.

In our patients, CS oxygen content fell during N_2O in 11 patients, with the mean showing a small but significant decrease. This suggests increased myocardial oxygen extraction. Even though the myocardium is depressed, the reduced coronary flow is not well-tolerated, with regional areas of greater oxygen extraction which is reflected in the smaller CS oxygen content. Supporting this conclusion are the lactate results with an increase in mean lactate concentration of coronary sinus blood. Mean lactate extraction also decreased significantly and in two patients lactate production was seen. These evidences of unbalancing of the myocardial oxygen supply-demand relationship were not accompanied by ST depression.

It must be pointed out that MVO_2 is a calculation and not a measurement and the fall in MVO_2 was almost entirely due to the decreased coronary flow. Hence in these patients MVO_2 does not reflect myocardial metabolic need. The latter is seen from the directly measured indicators of energy metabolism: the oxygen and lactate contents of coronary sinus blood. They revealed myocardia that were heading towards global ischaemia after 15 minutes of N_2O , without surgical stimulation to raise the blood pressure.

Our patients appeared to have more pronounced circulatory depression than those of previous studies.¹⁻³ No clear explanation exists but a possible factor is the presence of severe obstructive coronary disease, with reduced cardiac reserve. The effects observed may not have been solely due to the N₂O since it alone was tolerated better in another study of coronary patients.³ The haemodynamic changes may reflect additive effects of those from halothane.

In summary, fifteen minutes of 50 per cent N₂O, with 0.5 per cent halothane, given for 15 minutes to patients before CABG, caused a significant depression of the circulation and myocardial performance. The hypotension was due to decreased cardiac index, systemic resistance and heart rate. Coronary sinus oxygen content was reduced during N₂O and coronary sinus lactate content increased, indicating a trend towards compromised myocardial oxygenation. This trend was not identified by ST segment changes.

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Résumé

Les effets métaboliques et hémodynamiques myocardiques ont été observés en ajoutant 50 pour cent de protoxyde d'azote à 0.5 pour cent d'halotane à 13 patients avant l'incision chirurgicale de la graffe de l'artère coronaire. Le débit cardiaque et le débit sanguin du sinus coronaire furent déterminés avec la technique de thermodilution suivie de mesures hémodynamiques. Les mesures obtenues 15 minutes après l'addition de protoxyde d'azote ont démontré une baisse significative de la fréquence cardiaque, de la pression artérielle, de l'index cardiaque, du débit sanguin du sinus coronaire et de la consommation de l'oxygène myocardique. On observa une hausse significative du contenu lactate du sinus coronaire et une baisse significative de 27 à 11 pour cent, de l'extraction lactate myocardique. En conclusion, ces variations circulatoires doivent être causées par une dépression de la fonction ventriculaire par le protoxyde d'azote. Les myocardies de ces patients souffrant de graves malaises coronaires développèrent une ischémie coronarienne durant la période où ils reçurent 50 pour cent d'oxygène, alors qu'ils étaient hypotensifs. Le protoxyde d'azote ne devrait pas être administré lorsque l'hypotension est présente chez des malades souffrant de malaises coronaires.