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Haemodynamics during inhalation of a 50% nitrous-oxide-in-oxygen mixture with and without hypovolaemia

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Background: Inhalation of a gas mixture containing 50% nitrous oxide in oxygen (N_2O/O_2) is widely used for pain relief in emergency situations, which may also be associated with blood loss. The aim of this study was to evaluate the haemodynamic effects of this gas mixture in normo- and hypovolaemic subjects.
Methods: Six healthy males were studied during inhalation of N_2O/O_2 before and after withdrawal of 900 ml of blood. On each occasion, we measured systemic and pulmonary arterial pressures, cardiac output, blood gases, extravascular lung water, and the blood flow and oxygen consumption in the whole body, liver and kidneys.
Results: Inhalation of N_2O/O_2 reduced the stroke volume and increased peripheral resistance. Oxygen uptake decreased in the liver (−30%) and in the whole body (−23%). Blood withdrawal reduced the pulmonary arterial and central venous pressures (−30 to −50%) and further decreased stroke volume and the blood flows to the liver and the kidney (−15%). The extravascular lung water tended to increase both during inhalation of N_2O/O_2 and during hypovolaemia.
Conclusion: N_2O/O_2 aggravated the hypokinetic circulation induced by hypovolaemia. However, the oxygen consumption decreased only during inhalation of N_2O/O_2. This opens up the possibility that the cardiodepression associated with N_2O/O_2 is caused by a change in metabolic demands.

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Key words: Blood loss; central hemodynamics; kidney, blood flow; liver, blood flow; nitrous oxide; oxygen uptake.

INHALATION of a gas mixture containing equal amounts of nitrous oxide and oxygen (50%/50% of N_2O/O_2) is often used for pain relief in emergency situations and during ambulance transport. The prompt onset of analgesic action, low risk of overdose and the fact that administration is non-invasive and can be carried out by paramedics have contributed to the popularity of this treatment.

The haemodynamic effects of N_2O/O_2 have been studied during other forms of anaesthesia. They comprise a reduction of cardiac output and an increase in the peripheral resistance (1, 2). However, little is known about the haemodynamic effects of N_2O/O_2 in awake subjects. In particular, it is unclear whether the possible cardiodepression due to N_2O/O_2 would make this mixture unsuitable during hypovolaemia, which is common in emergency situations.

In the present report, we investigate the effects of N_2O/O_2 on the central and regional haemodynamics and on oxygen consumption in awake human volunteers. We also study how these effects are altered by hypovolaemia. Special attention is paid to the splanchnic and renal blood flows, which are sites of potential interactions between N_2O/O_2 and hypovolaemia. Splanchnic vasoconstriction has been reported after blood loss (3) and inhalation of N_2O/O_2 (4, 5). The renal blood flow is probably well maintained during moderate bleeding (6), but a reduction occurs during inhalation of N_2O/O_2 (5, 7).

Material and methods

We studied 6 healthy and athletic male firemen who fulfilled the criteria for blood donors in our hospital. Their mean age was 26 years (range 21–34), mean height 186 cm (range 183–192) and weight 79 kg (range 72–87) and all were experienced "paid volunteers" at the Department of Physiology at Huddinge University Hospital. They had given their informed consent to participate in the study, which was approved by the Local Ethics Committee. The purpose, extent and risks involved in the study were explained. Those who agreed to participate were further informed both orally and in writing about the study. It was pointed out that a volunteer could withdraw from participation at any time without giving any rea-

son for doing so. The study was performed at the Department of Physiology with full emergency equipment available and always in the presence of at least one anaesthesiologist. The entire experiment, including catheterizations and measurements, required about 4 hours. Blood sampling volumes were kept to a minimum but required about 150 ml of blood for each experiment.

Experimental procedure

After an overnight fast, the subjects were investigated in the morning lying comfortably on a bed. They were catheterized and, after a resting period of 30 min to achieve physiological steady state, they inhaled a mixture of 50% nitrous oxide and 50% oxygen during 30 min via a non-rebreathing anaesthesia circuit with a fresh gas flow of 7 l min^{-1}. Excess gas was evacuated from the room. Measurements were performed at the end of this 30-min period. Thereafter, they inhaled 100% O_2 during 5 min to prevent diffusion hypoxia. After that, 900 ml of blood (about 15% of the blood volume) were withdrawn using conventional blood donor equipment, which required about 20 min. The subject was then breathing either room air (n=3) or N_2O/O_2 (n=3) in the hypovolaemic state during another 30 min before the next measurement was performed. Finally, the subjects who had breathed normal air were given N_2O/O_2 during 30 min, and air was supplied to those who had breathed N_2O/O_2 (Fig. 1). The final measurement was performed, and the withdrawn red blood cells were returned.

The purpose of using a double protocol was to eliminate any time dependence of the pooled results. Thus, significant changes in the parameters could be disclosed only if the change occurred regardless of whether bleeding preceded the breathing of N_2O/O_2 or the opposite order of events was studied.

Measurements of haemodynamics were done at the end of the initial resting period and after each combination of N_2O/O_2 and blood withdrawal. The 30-min period with each treatment before measurements were performed was considered sufficient for physiological steady state to be established.

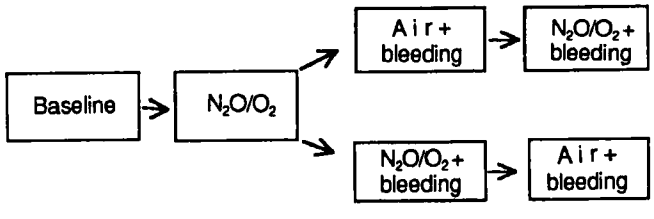

Fig. 1. Experimental design. Measurements were done at the end of each 30-min period, which is illustrated by a box.

Catheterization

A triple-lumen thermistor-tipped balloon catheter (Swan-Ganz®, Edwards Laboratories, Santa Ana, CA, USA) was introduced percutaneously using a sleeve technique into a medial cubital vein and was advanced under fluoroscopy to the pulmonary artery. This catheter was used for the measurement of cardiac output and pulmonary artery pressures. The femoral vein was punctured using a sleeve technique and a 7F Cournand catheter was advanced to the left renal vein under fluoroscopic guidance. By the same technique an 8F Cournand catheter was inserted from a femoral vein into the right hepatic vein.

Blood samples were collected from these catheters to measure the blood flows and the oxygen uptake in the kidneys and in the liver. A thermistor-tipped, fibreoptic catheter (Pulsion AG, Münich, Germany) was introduced percutaneously using a sleeve technique into the femoral artery and was advanced to the thoracic aorta under fluoroscopic control. It was used for the recording of extravascular lung water and central blood volume. The left brachial artery was also catheterized, as was a peripheral vein, for the continuous infusion of indocyanine green (8, 9) and para-amino hippuric acid (10, 11), which are standard methods for measurement of the splanchnic (liver) and renal blood flows.

Blood flow determinations

Cardiac output (CO) was measured by thermodilution (Edwards Laboratory model 5720) with injection of 10 ml cold (0 to +4°C) 5% glucose solution. The splanchnic (liver) and renal blood flows were determined by continuous indicator techniques, using indocyanine green and para-amino hippuric acid, respectively. The concentration of these indicators was 1.05 g l^{-1} and 15 g l^{-1}, respectively, and both were infused intravenously at a rate of 0.764 ml min^{-1} (0.802 mg min^{-1}). Forty-five minutes of continuous infusion were allowed for equilibration in the awake state. Blood flow was calculated by the Fick principle from the infusion rate of these indicators and the difference in their concentration between arterial blood and the blood in the hepatic and renal veins. Each reported blood flow determination used in the statistics was the mean of 3 to 5 measurements (8–11).

Pressure measurements

The pulmonary arterial pressure was recorded and, by inflating the balloon at the tip of the catheter, the vessel was occluded so as to allow measurement of pulmonary capillary wedge pressure. The central venous pressure was measured in the right atrium via a

side-hole in the catheter. The systemic arterial pressure was measured by means of the brachial artery catheter.

Volume measurements

The blood volume before the experiments was measured by the radio-albumin method (^{131}I-RIHSA) and the changes were estimated from the dilution of the blood haemoglobin concentration (B-Hb) after considering any loss of Hb (12, 13). The total thermal volume (TTV) (distribution volume for temperature between the injection point and sampling point, right atrium-thoracic aorta), central blood volume (CBV) (distribution volume for dye) and "extravascular lung water" (EVLW) were measured using a lung water computer system (Partig, System Cold, Münich, Germany). An indicator bolus of dye was dissolved in 10 ml glucose 5% (0–2°C) and injected within 1 s by a temperature-controlled syringe into the right atrium. The dilution curves for dye and temperature were obtained from the aorta with the thermistor-tipped fibreoptic catheter and recorded as a function of time by the computer, which calculated the mean transit times (MTT) for the indicators (14). The variables TTV, CBV and EVLW were then calculated as follows:

$$TTV = CO \times MTT \text{ thermo}; \quad CBV = CO \times MTT \text{ dye};$$
$$EVLW = TTV - CBV$$

The temperature of the injected solutions used in the calculations was corrected for catheter dead space, taking into consideration the different proportions of the catheter that lay intravascularly and in room air. All measurements were made 5 times, the injections being distributed randomly over the respiratory cycle.

Oxygen content of blood and oxygen uptake

The acid-base balance, blood gases, oxygen saturation and haemoglobin concentration of arterial and mixed venous blood were determined by spectrophotometry (OSM-2, Radiometer, Copenhagen, Denmark). Total body oxygen uptake was calculated as the product of cardiac output and the arterial-mixed venous oxygen content difference, and the splanchnic and renal oxygen uptakes were deduced from their blood flows and the arterial-hepatic venous and arterial renal-venous oxygen content differences.

Statistics

The results are presented as the mean and standard error of the mean (SEM). The changes from baseline were studied by repeated-measures analysis of variance (ANOVA), followed by Dunnett's test. Two-way factorial ANOVA was used to evaluate the separate effects of N_2O/O_2 and hypovolaemia on the measured physiological parameters. This test also detects interactions between N_2O/O_2 and hypovolaemia that increase or decrease their respective effects when combined. $P<0.05$ was considered statistically significant.

Results

Subjective effects

Inhalation of N_2O/O_2 caused a moderate sedation that was enhanced by hypovolaemia. One volunteer experienced euphoria from N_2O/O_2 and 2 reported transient nausea when hypovolaemia was induced. After the experiment, none of the volunteers con-

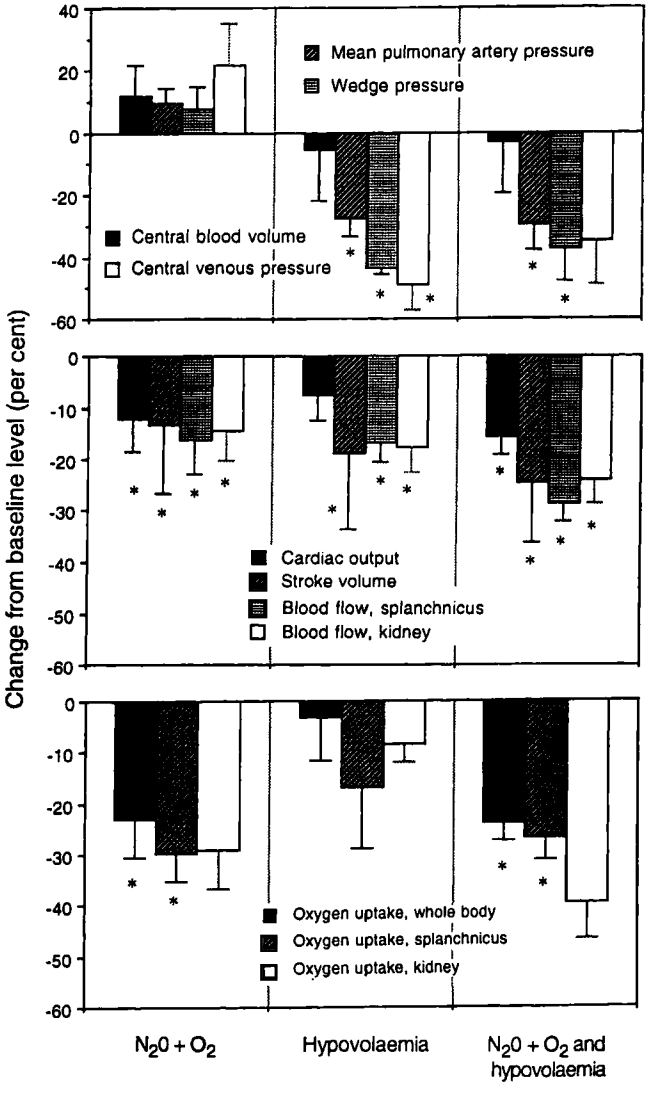

Fig. 2. Central haemodynamics (upper), *stroke volume and blood flows* (middle) *and oxygen uptake* (lower) *during experiments with N_2O/O_2 with and without hypovolaemia in healthy men. Data are mean±SEM. A significant change from baseline is indicated as follows:* * $P<0.05$.

Table 1

Central haemodynamics, extravascular lung water and blood volume in experiments with inhalation of a N_2O/O_2 mixture and with blood withdrawal in 6 healthy males (mean, SEM).

	Baseline	N_2O/O_2	Hypovolaemia	N_2O/O_2 and hypovolaemia
Systemic arterial pressure (mmHg)				
Systolic	112±3	116±3	113±4	108±3
Diastolic	66±2	69±1	65±4	63±4
Mean	83±2	89±4	84±4	81±4
Heart rate (bpm)	52±2	53±5	60±4	59±2
Cardiac output (l/min)	7.9±0.6	6.9±0.4*	7.2±0.3	6.6±0.4*
Stroke volume (ml)	151±7	131±7*	124±9*	114±10*
Central venous pressure (mmHg)	5.3±0.4	6.3±0.5	2.7±0.9*	3.5±0.7
Pulmonary artery pressure (mmHg)				
Systolic	19.7±0.9	20.3±0.8	14.0±0.9*	14.7±0.6*
Diastolic	10.2±0.6	10.3±0.4	6.0±0.7*	5.8±1.1*
Mean	13.7±0.7	14.8±0.4	9.5±0.6*	9.7±0.8*
Wedge	10.0±0.6	10.7±0.6	5.8±0.6*	6.2±0.9*
Pulm. vasc. resistance (mmHg·min/l)	0.47±0.03	0.60±0.08	0.55±0.08	0.62±0.15
Syst. vasc. resistance (mmHg·min/l)	10.0±0.7	12.3±1.0*	10.8±0.5	12.6±1.0*
Extravascular lung water (ml/kg)	5.7±0.2	7.3±0.8*	6.5±0.6	9.1±0.9*
Central blood volume (l)	2.19±0.31	2.45±0.47	2.08±1.21	2.13±0.35
Arterial B-Hb concentration (g/l)	149±4	151±4*	143±4*	143±5*
Total blood volume (l)	6.75±0.19	6.64±0.20	*6.10±0.18*	6.10±0.18*

* Difference from baseline significant at $P<0.05$ by ANOVA, followed by Dunnett's test.

sidered the N_2O/O_2 or the period of hypovolaemia to have been distressing. No complications occurred that could be related to the catheterizations.

N_2O/O_2 breathing

Inhalation of N_2O/O_2 alone reduced stroke volume (−13%) and increased the calculated systemic vascular resistance (+23%) but did not affect heart rate. Cardiac output and the splanchnic and renal blood flows decreased by between 13% and 16% (one subject with nausea had an increase in cardiac output). The systemic and pulmonary vascular pressures were essentially unaltered (Table 1, Fig. 2, upper and middle).

There was also a decrease in oxygen uptake by 23% in the whole body and by 30% in the splanchnic region. The mean oxygen uptake decreased by 29% in the kidney, but this was not significant (Fig. 2, lower). Arterial oxygenation was increased, as expected, during the breathing of N_2O/O_2. The acid-base balance was not affected.

Central blood volume increased in 5 of the 6 volunteers, which was not significant, but the extravascular lung water increased in all the volunteers (Table 1).

Hypovolaemia

The use of B-Hb as an indicator of dilution indicated that the withdrawal of 900 ml of blood decreased the blood volume by only 650 ml on average (−10%). The central blood volume, however, decreased by only about 100 ml (−5%).

Hypovolaemia was followed by a marked decrease in the pulmonary arterial pressure and the central venous pressure (−30% to −50%), while there were no changes in systemic arterial pressure. Stroke volume and the blood flows in the splanchnic region and in the kidneys remained significantly reduced (−17% to −18%), but the heart rate tended to rise (Table 1, 2).

Oxygen uptake was not significantly altered. Arterial oxygenation was as good as during baseline conditions, and there was no acidosis.

The central blood volume was essentially unaffected by the removal of blood. The extravascular lung water tended to increase (Table 1, 2).

N_2O/O_2 and hypovolaemia

The combination of N_2O/O_2 and hypovolaemia decreased stroke volume more than N_2O/O_2 alone ($P<0.05$), the total change being −24%. This was not fully compensated for by an increase in heart rate. All blood flows remained low, even lower than during N_2O/O_2 breathing or hypovolaemia alone. The effect on vascular pressures was the same as for hypovolaemia alone, and consisted in a reduction in pulmonary arterial and wedge pressures and essentially unaltered systemic arterial pressure. However, the sys-

Table 2

Blood flow and oxygenation in experiments with inhalation of a N_2O/O_2 mixture and with blood withdrawal in 6 healthy males (mean, SEM).

	Baseline	N_2O+O_2	Hypovolaemia	N_O+O_2 and hypovolaemia
Blood flow (l/min)				
Splanchnicus	1.43±0.07	1.20±0.13*	1.19±0.09*	1.03±0.09*
Kidney	1.57±0.07	1.33±0.08*	1.30±0.11*	1.18±0.06*
Arterial blood gases and acid-base balance				
pO_2 (kPa)	13.7±0.6	31.0±5.2*	13.4±0.8	34.1±1.7*
SO_2 (%)	98.2±0.4	99.2±0.2*	97.5±0.6	99.0±0.2*
pCO_2 (kPa)	5.4±0.2	5.2±0.6	5.3±0.3	5.3±0.6
pH	7.40±0.01	7.41±0.02	7.40±0.02	7.39±0.01
Standard HCO_3 (mmol/l)	24.5±0.3	24.3±0.8	24.0±0.3	23.7±0.3
Base excess	0.2±0.3	−0.5±0.3	−0.5±0.3	−0.5±0.5
A-V oxygen content difference (ml/l)				
Whole body	50.2±2.3	45.5±3.9	53.5±1.6	46.0±3.2
Splanchnicus	50.5±4.5	43.8±5.3	48.8±3.9	52.3±7.2
Kidney	15.0±0.4	11.9±3.7	16.8±1.4	11.3±3.3
Oxygen uptake (ml/min)				
Whole body	400±37	308±22*	387±21	304±27*
Splanchnicus	71±6	50±4*	59±8	52±6*
Kidney	24±2	17±6	22±3	14±5

* Difference from baseline significant by $P<0.05$ by ANOVA followed by Dunnett's test.

temic vascular resistance increased to the same level as during N_2O/O_2 breathing alone.

Oxygen uptake was reduced in the whole body as well as in the splanchnic region. The oxygen uptake in the kidneys decreased in 5 of the 6 volunteers. These changes were similar to those observed during N_2O/O_2 breathing (Fig. 2, lower). Arterial oxygenation was also as good as during N_2O/O_2 breathing alone, and there were no signs of acidosis.

The central blood volume remained unchanged compared to baseline, but the extravascular lung-water volume increased significantly to become greater than during N_2O/O_2 breathing or hypovolaemia alone (Table 1, 2).

The separate effects of N_2O/O_2 and hypovolaemia on the haemodynamic parameters at all points in time were analysed by two-way analysis of variance. The results showed that both N_2O/O_2 and hypovolaemia acted as independent predictors when reducing stroke volume and the blood flows to the the liver and kidney. No interactions between these parameters were found (Table 3).

Table 3

Two-way analysis of variance for the sparate effects of N_2O/O_2 and hypovolaemia on physiological parameters. Although $P<0.05$ was considered significant in this study, effects having a significance level of between $P<0.10$ and $P<0.05$ are also displayed. The significance level is shown and the direction of each change is indicated by an arrow.

	N_2O/O_2	Hypovolaemia
Heart rate		0.08↑
Cardiac output	0.07↓	
Stroke volume	0.09↓	0.02↓
Central venous pressure		0.001↓
Pulmonary artery pressure		0.001↓
Peripheral resistance	0.03↑	
Extravascular lung water	0.01↑	0.08↑
Splanchnic blood flow	0.06↓	0.04↓
Renal blood flow	0.03↓	0.01↓
pO_2	0.001↑	
SO_2	0.003↑	
HCO_3^-		0.08↓
Oxygen uptale, whole body	0.005↓	
Oxygen uptake, liver	0.04↓	
Oxygen uptake, kidney	0.09↓	

No interactions were found.

Discussion

N_2O/O_2 breathing

The present study confirms that inhalation of N_2O/O_2 decreases cardiac output (1, 2) and the blood flow to the splanchnic region and the kidneys (4, 5). However, the decrease in the arteriovenous difference for oxygen content suggests that the decrease in blood flow was due to reduced oxygen consumption.

This view constitutes an important adjunct to previous reports, in which the haemodynamic effects of N_2O/O_2 have usually been thought to reflect direct cardiodepression. Our data open up the possibility

that much of the cardiodepression associated with N_2O/O_2 is secondary to a change in the metabolic rate which reduces the need for oxygenated blood in several important organs.

The same metabolism-induced change of blood flow might also account for the increase in peripheral vascular resistance. Alternatively, it is associated with the mild sympathomimetic effect exerted by N_2O (15).

Hypovolaemia

The haemodilution indicated that the blood volume decreased only by 2/3 of the withdrawn volume, which suggests that capillary refilling operated as a physiological defence mechanism against hypovolaemia. Diffusion of fluid from the interstitial compartment to the blood vessels is believed to occur very slowly in non-hypotensive bleeding (12). The rate of capillary refilling in the present study was much faster, however, and is more consistent with that previously observed during hypotensive bleeding in the dog (16).

Withdrawal of blood still resulted in a hypokinetic circulation but, as expected, the systemic vascular pressures remained normal. Pulmonary vascular pressures, on the other hand, were reduced, and there was no significant increase in pulmonary vascular resistance. The fall in renal blood flow induced by the withdrawal of blood is interesting because there is little comparable data on humans and most animal studies indicate that this flow may be preserved (6).

N_2O/O_2 and hypovolaemia

The design of the study is such that the haemodynamic responses to inhalation of N_2O/O_2 and to blood loss can be studied separately, as well as in combination. One important result of our statistical analyses is the lack of interactive effects between N_2O/O_2 and hypovolaemia. Thus, the influence of these parameters on haemodynamics can be regarded as the sum of them.

This means that strong physiological effects may occur only when the direction of the changes induced by N_2O/O_2 and hypovolaemia are the same. In particular, inhalation of N_2O/O_2 aggravates the hypokinetic circulation induced by hypovolaemia. However, the oxygen uptake in the tissues was down-regulated by N_2O/O_2, but not by blood loss. Therefore, blood loss imposes a risk of peripheral hypoxaemia whereas this is not the case with the reduction of blood flow caused by N_2O/O_2. On the other hand, the present results illustrate that a blood loss of 900 ml is not enough to create hypoxaemia, as no metabolic acidosis became evident.

Central blood volume

The central blood volume increased slightly during the inhalation of N_2O/O_2 in most volunteers, the average change for the entire group being 0.26 l. This suggests that N_2O/O_2 does not contribute to the shift of blood from the thoracic cavity previously described during general anaesthesia with halothane and muscle paralysis (17). Bleeding was also followed by a marginal change in central blood volume, despite a decrease in the total blood volume of 10%. The net effect of N_2O/O_2 and hypovolaemia combined on the central blood volume was preservation of the volume compared to baseline. Why the central blood volume is maintained or even increased under the different conditions in the present study is not clear. It may be due to either differences in vascular tone in different vascular beds or simply to a reduced cardiac output, promoting right-heart filling.

Practical implications

Our study gives little reason to withhold N_2O/O_2 from patients during transport to hospital. The reduction of blood flow is probably beneficial during haemorrhage; if the delivery of blood is also limited to the injured site, the total loss of blood should be reduced. In addition, hypoxia in vital organs is countered by the breathing of 50% O_2. The reduced oxygen uptake from breathing N_2O/O_2 may also have a protective effect on tissue oxygenation. Despite the reduced blood flows, the combination of N_2O/O_2 and hypovolaemia did not increase the arteriovenous difference in oxygen content above baseline values.

One should note, however, that the present study was performed in young men in good physical condition. Possible contraindications for N_2O/O_2 still include patients with coronary arterial occlusions, who may show signs of a failing heart (18) and myocardial ischaemia (19) when used during general anaesthesia. Furthermore, the tendency for N_2O/O_2 to pool blood in central parts of the body and to increase the extravascular lung water might be unsuitable in patients with severe congestive heart disease. In addition, caution is advisable in those with suspected brain oedema, since N_2O/O_2 is known to increase the cerebral blood flow (5, 20).

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