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Effects of Nitrous Oxide on Contractile Function and Metabolism of the Isolated Heart

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Nitrous oxide has a long clinical history, but its effects on the heart remain controversial. The direct effects of N_2O on global myocardial function have not been reported. The authors' aim was to examine the inotropic, chronotropic, dromotropic, and vascular effects of N_2O, compared with its N_2 control, on hearts isolated from the guinea pig. Hearts (N = 31) were isolated and perfused at 37° C with Krebs-Ringer solution at constant pressure. Isovolumetric left ventricular pressure (LVP) and its derivative (maximum rate of tension development [dP/dt_{max}]) were measured by placing a saline-filled, latex balloon into the left ventricle. Bipolar electrodes were placed in the right atrium and right ventricle for measurement of heart rate (HR) and atrioventricular conduction time (AVCT). The venae cavae were ligated, and the right ventricle was cannulated through the pulmonic valve to collect coronary sinus effluent for measurement of coronary outflow O_2 tension, adenosine, and inosine. After stabilization and perfusion with 96% O_2 (plus 4% CO_2), each heart was exposed for 10 min either to 48% N_2O or to 48% N_2 with 48% O_2. After repeated perfusion with 96% O_2 for 10 min, hearts were exposed in the reverse order to 48% N_2O or 48% N_2. In the postcontrol period, hearts were again exposed to 96% O_2. Inflow P_{O_2} (in mmHg) was 506 ± 5 (standard error of the mean [SEM]) during 96% O_2 and 258 ± 5 during both 48% N_2 and 48% N_2O. Effluent P_{O_2} was 155 ± 7 during 96% O_2, 81 ± 5 during 48% N_2, and 83 ± 5 during 48% N_2O. Adenosine increased coronary flow maximally 95 ± 5% in arrested and 50 ± 9% in paced hearts. Compared with in the O_2 controls, N_2 significantly increased coronary flow 26 ± 3%, reduced O_2 delivery 36 ± 2%, depressed LVP 20 ± 2% and $+dP/dt_{max}$ 15 ± 2%, and decreased myocardial O_2 consumption 36 ± 3%; effluent concentrations of adenosine and inosine increased 4.8 ± 0.8 and 2.7 ± 0.6 times. N_2 alone did not alter HR, AVCT, percentage O_2 extraction, or the O_2 supply-to-demand ratio. Substitution of 48% N_2O for 48% N_2 produced no additional change in these variables except for significant additional 5 ± 2% decreases in LVP and $+dP/dt_{max}$. N_2O had no appreciable direct effects in addition to those of N_2 on coronary flow or O_2 consumption. Although the mild hypoxia caused by 48% N_2 or N_2O decreased contractility and O_2 consumption and increased effluent release of adenosine and inosine, the increase in coronary flow was substantially less than maximal flow attained with adenosine. This suggests that reduced O_2 content, like reduced coronary flow, can itself potentially limit cardiac work. The findings also demonstrate that N_2O adds little to the cardiac effects of reduced O_2 delivery except for a significant depression of contractility. The authors speculate that, *in vivo*, N_2O may also be a mild direct cardiac depressant, especially in the presence of other cardiac depressant agents. (Key words: Anesthetics, gases: nitrous oxide. Animal: guinea pig. Heart: coronary flow; electrophysiology; isolated; left ventricular pressure; oxygen consumption.)

NITROUS OXIDE has been used as an incomplete anesthetic for more than 140 years. It is not a potent anesthetic, and its cardiovascular effects at clinical inspired concentrations of up to 70% with O_2, at most, appear minimal.[1–4] It is controversial whether N_2O is a negative inotropic agent. Several *in vitro*[5–7] and *in vivo* animal[8] and human[2,3] studies suggest that N_2O can depress cardiac function; other studies, however, suggest that N_2O does not depress cardiac function.[4,9,10] In most *in vivo* studies other anesthetic agents or adjuvant drugs were administered and extracardiac factors could not be adequately controlled to test the direct effects of N_2O alone on cardiac function. Moreover, many studies have not used N_2 as a control for N_2O; cardiac depression in these studies could reflect an indirect inotropic effect secondary to relative hypoxemia, compared with high O_2 controls, rather than a direct effect of N_2O.

There are no known studies of the direct, global effects of N_2O on spontaneous atrial rate, atrioventricular (AV) conduction time, isovolumetric left ventricular pressure (LVP) and its development, coronary flow, myocardial O_2 extraction, and the O_2 supply-to-demand ratio. Our aim was to carefully examine the direct mechanical and metabolic effects of 48% N_2O, compared with the effects of 48% N_2; the mildly hypoxic effects of 48% N_2 and N_2O were compared with the control responses of 96% O_2. The isolated Langendorff heart preparation was selected for study so that intrinsic, mechanical, humoral, and autonomic nervous system influences of N_2O could be avoided.

Materials and Methods

After the Animal Studies Committee approval was obtained, 31 albino English short-haired guinea pigs (400–600 g) were injected interperitoneally with 10 mg of ketamine and 1,000 units of heparin and were decapitated when unresponsive to noxious stimulation. After thoracotomy, the inferior and superior venae cavae were cut

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and the aorta was cannulated distal to the aortic valve. The heart was immediately perfused retrogradely through the aorta and was excised. All hearts were perfused at an aortic root perfusion pressure of 55 mmHg. The perfusate, a modified Krebs-Ringer solution, was filtered in-line (Astrodisc®, Gelman Sciences, Ann Arbor, MI, 5-μm pores) and had the following composition (millimolar): Na^+ 137, K^+ 5.9, Mg^{2+} 1.2, Ca^{2+} 2.5, Cl^- 134, HCO_3- 15.5, H_2PO_4- 1.2, glucose 11.5, mannitol 16, EDTA (ethylenediaminotetraacetic acid) 0.05, and insulin 5 units/l. Perfusate and bath temperature were maintained at 36 ± 0.3 °C with the use of a thermostatically controlled water circulator (Haake E 52®, Haake Buchlar, Saddle Brook, NJ). During control periods (normoxia), the solution was equilibrated with a gas mixture of 96% O_2 and 4% CO_2 at a flow rate of 3 l/min. In all studies 4% CO_2 constituted the balance of the gas mixtures.

Systolic LVP was measured isometrically with a transducer (Gould-Statham P23®, Gould Electronics, Elk Gove, IL) connected to a thin, saline-filled latex balloon (Hugo Sachs Electronic, KG, Federal Republic of Germany) inserted into the left ventricle through the mitral valve from a cut in the left atrium. Balloon volume was adjusted to maintain a diastolic LVP of 0 mmHg during the initial control period; rates of tension development ($+dP/dt_{max}$ and $-dP/dt_{max}$) were measured from the derivatives of LVP obtained electronically. Two pairs of bipolar electrodes (Teflon®-coated silver, diameter 125 μm) were placed in each heart to monitor intracardiac electrograms from which spontaneous sinoatrial rate and AV conduction time were measured. The two electrode signals were amplified and displayed continuously on an image-storing oscilloscope (5A26N, 5B12N, Tektronix, Beaverton, OR). Atrial rate was determined from the right atrial beat-to-beat interval, and AV conduction time was determined from the superior right atrial to right ventricular pulmonary conus beat-to-beat interval. Electrogram intervals were measured automatically on-line by digital timer systems that allowed instantaneous interval and rate analyses.

Coronary sinus effluent was collected by placing a cannula into the right ventricle through the pulmonic artery after ligation of the venae cavae. Samples (4 ml) were collected and immediately frozen for later determination of adenosine and inosine by high-pressure liquid chromatography. Coronary inflow (aortic) was measured at a constant temperature by an electromagnetic flow meter (Biotronix® BL610-2A with Series 2000C® extracorporeal transducer, 1.5 mm ID, Biotronix Laboratories, Kensington, MD) that was calibrated daily by four-point, timed collections into a volumetric cylinder over the flow range of 0–24 ml/min. Calibration curves were best fit by nonlinear regression analysis ($r^2 > 0.98$). Zero inflow was periodically established by temporarily bypassing the flow transducer.

Coronary inflow and outflow (coronary sinus) O_2 tensions were measured continuously on-line (Instech® 203B, Instech Laboratories, Plymouth Meeting, PA) and verified off-line with a intermittently self-calibrating analyzer system (Radiometer® ABL-2, Medtron Chicago, Des Plaines, IL). The in-line, temperature-controlled, miniature Clark electrodes were calibrated periodically with the use of a bypass circuit in which perfusate was gassed with 100% N_2, 21% O_2, and 96% O_2 to adjust O_2 tension to 20, 150, and 600 mmHg, respectively. These hearts depend solely on the crystalloid solution from which to extract dissolved O_2. O_2 delivery was calculated from the inflow O_2 tension × O_2 solubility (24 μl per ml saline per 760 mmHg) × coronary flow per gram wet heart tissue (average 1.83 ± 0.05 g, standard error of the mean [SEM]). Percentage O_2 extraction was calculated as follows: 100 × the difference between inflow and outflow O_2 tensions ÷ inflow O_2 tension. Myocardial O_2 consumption was calculated as follows:

O_2 solubility × coronary flow/gram

× (the inflow O_2 − outflow O_2 tension difference)

Electrograms, heart rate (HR), AV conduction time, outflow O_2 tension, coronary flow, LVP, and perfusion pressure were tape recorded (Vetter D1®, Vetter, Rebersburg, PA) for later detailed analysis of these data and for measurement of LV dP/dt_{max}. All measured variables were displayed on a fast-writing (3-kHz), thermal array eight-channel recorder (Astro-Med® MT9500, Astro-Med, West Warwick, RI). Derived variables were computed with the use of a Microsoft Excel® (Microsoft, Redmond, WA) software program.

Protocol and Statistical Analysis

After stabilization and perfusion with 96% O_2 (normoxia), each heart was first exposed, in random order, either to 48% N_2 or 48% N_2O (mild hypoxia) for 10 min. After a 10-min return to control (96% O_2), each heart was perfused for 10 min with 48% N_2 or 48% N_2O in the reverse order. Individual data obtained for each variable were placed into four groups: initial controls (96% O_2); 48% N_2; 48% N_2O; and 96% O_2 (postcontrol). Because each heart was exposed twice to N_2 and N_2O, the two values for N_2 and for N_2O per experiment were averaged and treated as single data points for statistical analyses. This was done to reduce a potential bias for time-related and/or reduced O_2 delivery-dependent effects. There was no significant difference in the variable means obtained from the double exposures to N_2 and to N_2O (paired t tests, data not shown). Adenosine (0.2 ml of 200 μM solution) was injected intracoronarily during the initial control period and during the final O_2 control period to assess maximal coronary flow in arrested hearts; during the final O_2 control period, hearts were also paced at 220 beats per min to assess maximal flow in contracting hearts so that the effect on coronary flow with compression of the coronary vasculature could be considered.

TABLE 1. Changes in Cardiac Variables with Exposure to 96% O_2, 48% N_2, and 48% N_2O

	Control 96% O_2	48% N_2	48% N_2O	Postcontrol 96% O_2
Heart rate (beats per min)	220 ± 3	222 ± 3	220 ± 3	222 ± 3
AV conduction time (ms)	57.1 ± 1.0	59.5 ± 1.1	60.1 ± 1.4	58.0 ± 1.0
O_2 delivery ($\mu l \cdot g^{-1} \cdot min^{-1}$)	90 ± 4	58 ± 2*	57 ± 2*	96 ± 4
O_2 extraction (%)	69.3 ± 1.4	68.6 ± 2.0	68.0 ± 1.9	71.4 ± 1.9
Adenosine (pmol/ml)	6 ± 2	28 ± 6*	25 ± 5*	—
Inosine (pmol/ml)	45 ± 8	123 ± 27*	154 ± 32*	—

The order of N_2 and N_2O were randomized and then repeated in reverse order after reexposure to 96% O_2 (data not shown). Balance of 96% O_2 gas is 4% CO_2; balance of N_2 and N_2O gases are 48% O_2 and 4% CO_2.

N = 31; *$P < 0.05$ *versus* 96% O_2 controls. All values are mean ± SEM.

All data are expressed as means ± SEM. The effects of N_2O were tested against the effects of N_2 and O_2. Measurements were made during the last minute of a 20-min initial O_2 control period, a 10-min exposure to N_2 or N_2O, a 10-min exposure to N_2O or N_2 (reversed order), and a 20-min final O_2 postcontrol period. Statistical differences among groups for each variable were determined by two-way analyses of variance (Statview® [Abacus Concepts, Calabasus, CA] and CLR anova® [Clearlake Research, Houston, TX] software programs; Macintosh® SE30 [Apple Computer, Cupertino, CA] computer); if F tests had significant results, Fisher's least significant difference tests were used to compare means. Mean values were considered significant at $P \leq 0.05$.

Results

Inflow (aortic) *p*H, P_{CO_2}, and P_{O_2} were 7.52 ± 0.02, 29 ± 4 mmHg, and 506 ± 5 mmHg, respectively, for 96% O_2, and were similar—7.54 ± 0.02, 28 ± 1 mmHg, and 258 ± 5 mmHg, respectively—for 48% N_2 and 48% N_2O. Outflow (coronary sinus) *p*H, P_{CO_2}, and P_{O_2} values were 7.36 ± 0.02, 36 ± 2 mmHg, and 155 ± 7 mmHg, respectively, for 96% O_2 (initial control); postcontrol O_2 values were not significantly different from initial O_2 control values.

Table 1 shows mean values for several cardiac variables during perfusion with O_2, N_2, and N_2O. Neither N_2 nor N_2O produced any changes in HR, AV conduction time, or percentage O_2 extraction. During exposure to N_2 or N_2O, O_2 delivery decreased (−36 ± 2%) and the effluent concentrations of adenosine and inosine increased significantly for these variables; the differences between effects produced by N_2 and N_2O were not significant.

Figures 1–6 display effects of partial substitution of O_2 with N_2 or N_2O on other cardiac variables. Figure 1 shows that coronary flow was increased similarly (26 ± 3%) with N_2 and N_2O and that the increases in flow were much less than those produced by bolus injections of adenosine that produced maximal vasodilatation in arrested (95 ± 5%) and paced (50 ± 9%) hearts. Figures 2 through 4 show that N_2 significantly decreased systolic LVP (−20 ± 2%) and its peak positive (−15 ± 2%) and negative (−19 ± 3%) derivatives. N_2O also significantly decreased peak LVP (−20 ± 2%) and its peak positive derivative (−20 ± 2%). The greater decreases in LVP and $+dP/dt_{max}$ with N_2O than with N_2 were statistically significant; the decreases in $-dP/dt_{max}$ were not significantly different. Figure 5 shows that myocardial O_2 consumption was depressed similarly by N_2 and N_2O. The proportionate decreases in O_2 delivery (−36 ± 2%) and O_2 consumption (−36 ± 3%) during exposure to N_2 and N_2O are reflected in figure 6 by the unchanged ratio of O_2 supply to O_2 demand.

Discussion

Our results in the isolated perfused guinea pig heart demonstrate that, compared with in O_2 controls, 48% N_2 produces a mild hypoxia; this is demonstrated by the submaximal increases in coronary flow and effluent release of adenosine and inosine; by the decreases in O_2 delivery, myocardial O_2 consumption, and systolic isovolumetric

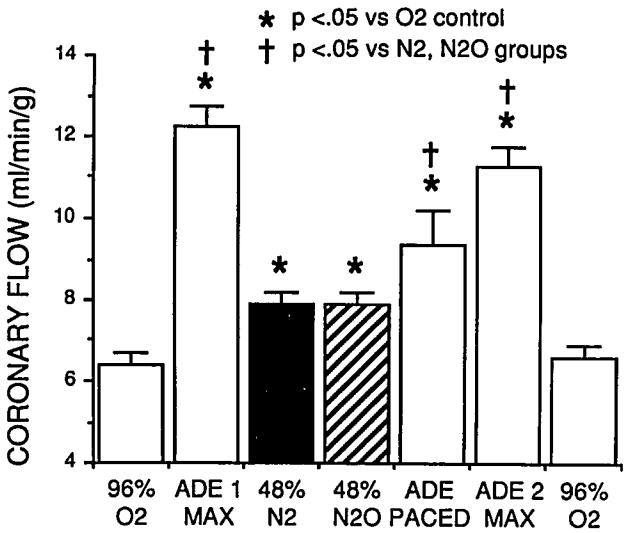

FIG. 1. Effects of adenosine (ADE), N_2, and N_2O on mean coronary flow. Adenosine was given before and after exposure to N_2 and N_2O and during pacing at 250 beats per min. The order of exposure to N_2 and N_2O was randomized. After reexposure to 96% O_2 (data not shown), hearts again were exposed to N_2 and N_2O, but in the reverse order. Note that N_2 and N_2O did not maximally increase coronary flow. Number of hearts = 31.

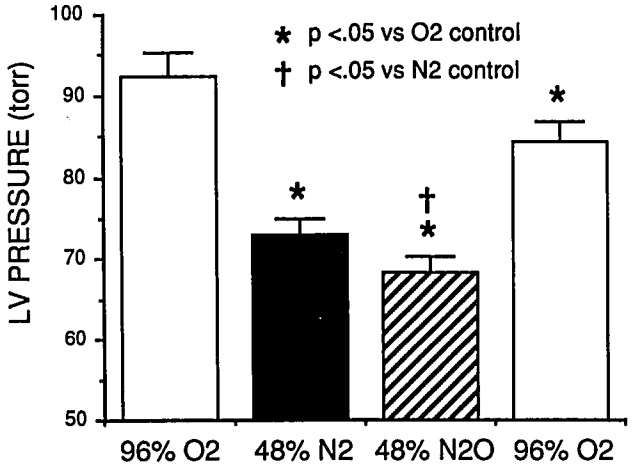

FIG. 2. Effects of N_2 and N_2O on peak isovolumetric left ventricular (LV) pressure. (See figure 1 for details).

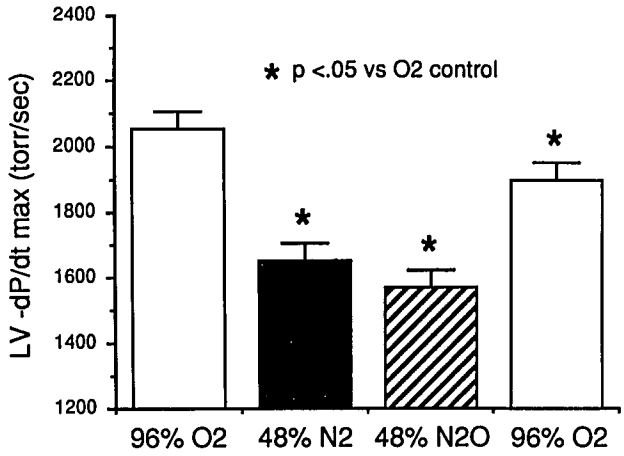

FIG. 4. Effects of N_2 and N_2O on the negative derivative of isovolumetric left ventricular (LV) pressure.

LVP; and by its rates of development and relaxation. Forty-eight percent N_2, however, did not alter HR, AV conduction time, percentage O_2 extraction, or the O_2 supply-to-demand ratio. This indicated that mild hypoxia, resulting from 48% N_2 alone, had little adverse effect on the sinoatrial pacemaker rate or AV conduction. It is interesting that the reduced inflow O_2 tension was not balanced by a sufficient increase in flow to maintain oxygen delivery even though maximal flow was not attained. Because percentage O_2 extraction did not increase, myocardial O_2 consumption ($M\dot{V}_{O_2}$) was necessarily decreased.

Given these baseline effects of mild hypoxia, substitution of N_2O for N_2 produced no additional changes in these variables from their N_2 controls except for small but significant decreases in peak LVP and its maximal positive derivative. Our *in vitro* study confirms that N_2O, in concentrations used clinically, is indeed a mild depressant of cardiac contractility during mild hypoxia. They also show that N_2O has no appreciable effect on the rate of sinoatrial automaticity or AV conduction and no effect different than that of N_2 on coronary flow, O_2 consumption, or the O_2 supply-to-demand ratio.

CARDIAC EFFECTS OF N_2 *VERSUS* O_2

Perfusion of these hearts with the control solution (96% O_2) allows for a stable preparation with a coronary flow reserve twice that of the baseline flow. Although the delivery of O_2 is less than *in vivo* because O_2 is only carried dissolved in solution, the decrease in viscosity, the lack of external work (afterload impedance), and sympathetic denervation decrease the metabolic needs of the heart; lactate is not produced.[11] A potential disadvantage of this preparation is that mild hypoxia, *per se*, causes a reduction in cardiac work. Only one level of normothermic hypoxia (48% N_2) was examined with which to compare the effects

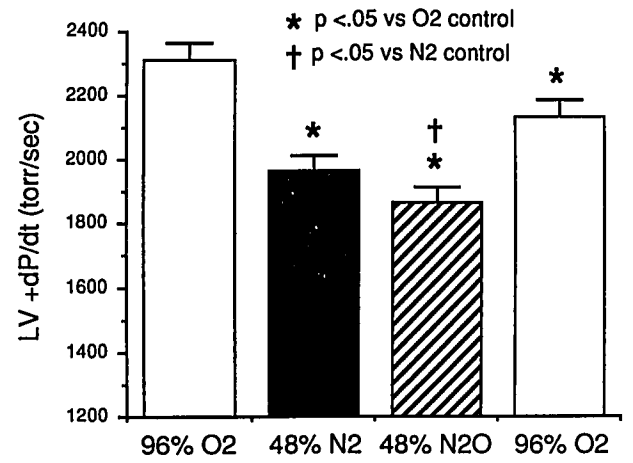

FIG. 3. Effects of N_2 and N_2O on the positive derivative of isovolumetric left ventricular (LV) pressure.

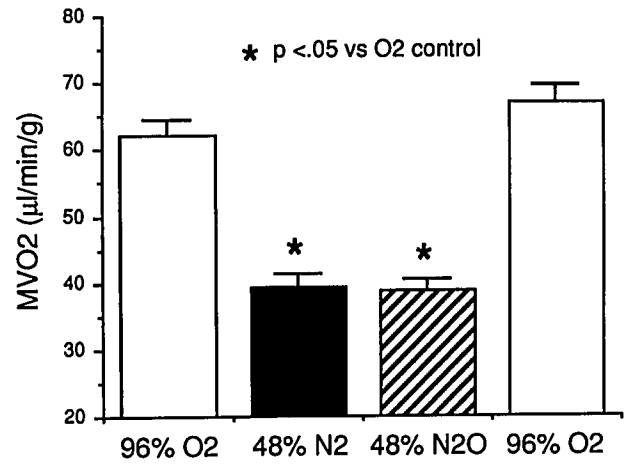

FIG. 5. Effects of N_2 and N_2O on myocardial oxygen consumption ($M\dot{V}_{O_2}$).

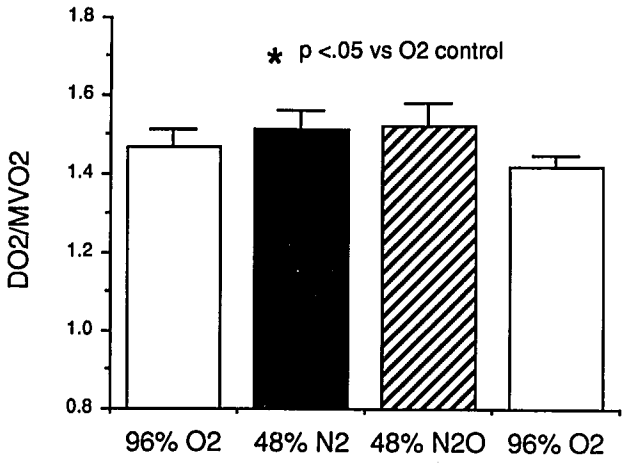

FIG. 6. Effects of N_2 and N_2O on the O_2 supply to demand ratio. $\dot{D}_{O_2}$ = oxygen delivery; $\dot{M}\dot{V}_{O_2}$ = myocardial oxygen consumption.

of N_2O because a lesser degree of relative hypoxia would necessarily correspond to a lower concentration of N_2O and because a greater degree of hypoxia might compromise cardiac function with reoxygenation.[12] Because these hearts depend solely on the crystalloid solution from which to extract dissolved O_2, if O_2 extraction reaches a maximum, the O_2 needs of the heart can be met only by an increase in coronary flow.

An interesting finding of this study, however, is that 48% N_2 (as well as 48% N_2O) caused depressions of $\dot{M}\dot{V}_{O_2}$ and contractile function, whereas coronary flow only submaximally increased (25%) as shown by the greater increase in flow (50%) with adenosine given to paced hearts. Coronary sinus O_2 content decreased, but the percentage extraction of O_2 did not change. The decrease in $\dot{D}_{O_2}$, despite the increase in flow, was matched by a similar decrease in $\dot{M}\dot{V}_{O_2}$ so that the $\dot{D}_{O_2}/M;\dot{V}_{O_2}$ ratio did not change significantly. We have demonstrated previously in a similar preparation[13] that, beyond a threshold of arterial hypoxia, $\dot{D}_{O_2}$ and $\dot{M}\dot{V}_{O_2}$ fall together even though coronary flow is not maximal; this was shown by additional increases in flow with increasing concentrations of exogenous adenosine. $\dot{D}_{O_2}$, rather than coronary flow, therefore, may be a potentially rate-limiting factor in cardiac work under certain conditions. $\dot{M}\dot{V}_{O_2}$ might decrease because the induced decrease in $\dot{D}_{O_2}$, despite the increase in flow, becomes inadequate to maintain cardiac function at the same level. Although coronary flow (supply) is believed to be tightly coupled to cardiac metabolism (demand), other factors independent of flow, such as reduced O_2 content, can affect cardiac function.

That $\dot{M}\dot{V}_{O_2}$ may be limited by $\dot{D}_{O_2}$ is demonstrated by steep O_2 gradients within the myocyte and by optical measurements of cytochrome aa_3 redox states *in vitro*.[14,15] A parallel to this notion is the finding that, in many *in vitro* studies, it has been demonstrated that expected changes in adenosine triphosphatase (ATP), adenosine diphosphate (ADP), and inorganic phosphate (P_i) values are not observed with alterations in cardiac work.[15,††] Even in oxygenated *in vivo* dog hearts it was recently shown[16] that induced increases in $\dot{M}\dot{V}_{O_2}$ are not necessarily correlated with increases in free phosphate metabolites (ADP and P_i) of ATP hydrolysis; moreover, the phosphorylation potential ($ATP/[ADP + P_i]$) decreased only when the increase in $\dot{M}\dot{V}_{O_2}$ was not matched by an increase in $\dot{D}_{O_2}$. This suggests that arterial O_2 content can limit oxidative phosphorylation to produce a decline in cardiac work rather than, or in addition to, a limitation of coronary flow.†† This could primarily be a result of a limiting of O_2 diffusion between capillaries and mitochondria directly or could secondarily result from a depletion of energy substrates. In the current study, the moderate increases in release of adenosine and inosine with the reduction in O_2 content also suggest that cellular respiration was impaired. However, much larger increases (four to five times more than with 48% N_2) are observed with exposure to 96% N_2 (unpublished results). Thus, the depressant effects of mild hypoxia coupled with the submaximal increase in coronary flow suggest that the capacity to vasodilate was not the primary or only factor limiting cardiac function and $\dot{M}\dot{V}_{O_2}$. It appears that under some circumstances lowered O_2 tension, or content, must also be considered to directly limit myocyte respiration in lieu of the underutilized capacity to increase coronary flow to enhance O_2 delivery.

N_2O Effects on Contractility

The many years of clinical experience with N_2O indicate that it may have mild cardiovascular depressant effects that may be partially counterbalanced by a simultaneous reflexly mediated increase in sympathetic tone. The few studies in which 40–60% N_2O with O_2 was the sole anesthetic administered to healthy humans used noninvasive tests (ballistocardiography, echocardiography, left ventricular ejection time) or indirect invasive tests (aortic pulse–pressure curves) to detect changes in cardiac contractility. These studies showed small increases,[1] small decreases,[2,3] or no change[4] in these indices of contractility. In an acute dog study, a small increase in cardiac output with no change in LVP was reported when 75% N_2O was administered with 1% halothane in O_2[9]; in another study, in which dogs were given pentobarbital and ventilated with 70% N_2O *versus* 70% N_2, a small decrease in cardiac output was found.[8]

Reflex changes in HR secondary to sympathetic stimulation and changes in atrial preload and aortic afterload impedance in all of these studies, as well as administration

†† Balaban RS, Heineman FW: Interaction of oxidative phosphorylation and work in the heart, in vivo. News in Physiological Sciences 4:215–218, 1989.

of other anesthetics and adjuvant drugs in some studies, severely complicate interpretation of the direct myocardial depressant effects of N_2O. Exposure of humans to 1.1–1.8 atm of N_2O alone in a hyperbaric chamber is associated with signs of increased sympathetic nervous system activity.[17,18] It has been demonstrated recently in humans that 40% N_2O causes activation of efferent sympathetic traffic directed to vascular smooth muscle and attenuation of baroreflex-mediated tachycardia.[19]

Only a few *in vitro* studies on direct cardiac effects of N_2O have been reported. Exposure of rat trabecula muscle to 50% N_2O with O_2 depressed contractility similarly to that of 50% N_2 with O_2 at 37° C.[5] At 25° C, however, 50% N_2O was found to depress cat papillary muscle about 22% more than 50% N_2.[10] In guinea pig right papillary muscle, depression of peak isometric tension and its maximal development by 50% N_2O *versus* 50% N_2 at 30° C and at 37° C was recently reported.[6] In dog papillary muscle perfused with blood from a donor dog, ventilation of the donor dog with 80% N_2O and 20% O_2 decreased contractility 25% compared with ventilation with room air.[7]

In the absence of autonomic influence or changes in preload and afterload, all of which can alter the effective force developed intrinsically by myocardial fibers, isovolumetric LVP and its peak positive and negative derivatives are good indices of intrinsic myocardial contractility. Our *in vitro* global heart study shows that 48% N_2O, compared with its 48% N_2 control, additionally depresses peak left ventricular isovolumetric pressure and its positive peak derivative, but only by about 5%. By randomizing and repeating in reverse order the exposures to N_2 and N_2O with O_2 controls, the added, albeit small, negative inotropic effect of N_2O in the isolated heart appears confirmed.

N_2O Effects on Automaticity and Conduction

In human studies, N_2O has been shown to increase,[1,17–19] decrease,[2,4] or produce no change[3] in HR. Because the HR response varies with autonomic tone and baroreflex activation, these studies have not truly addressed the direct effects of N_2O on automaticity. No adverse effects of N_2O on AV conduction time have been reported, but AV dissociation with AV junctional rhythm has been reported to occur during administration of N_2O with a volatile anesthetic, to be convertible to sinus rhythm with discontinuation of N_2O, and to return with readministration of N_2O.[20] However, AV dissociation might not necessarily be a direct effect of N_2O, but rather a result of a change in sympathetic nervous activity. In our *in vitro* study, we found that N_2O compared with N_2 (or with O_2) has no direct effects on either the intrinsic atrial rate or on AV conduction time and that its administration is not associated with any dysrhythmias.

N_2O Effects on Coronary Flow and Myocardial O_2 Consumption

The direct effects of N_2O on coronary vascular tone and myocardial O_2 consumption have not been well studied. N_2O is not reported to greatly alter coronary flow in acute dog studies.[8,21] Substitution of 60% N_2O for N_2 has been reported to constrict dog epicardial coronary arteries as assessed by angiography,[22] but 60–70% N_2O produced no change in coronary blood flow or myocardial O_2 consumption. In our study, the mild hypoxia caused by N_2 dilated the coronary bed, as reflected by a 25% increase in flow. However, this 25% increase above baseline flow was only about 25% and 50% of the coronary reserve flow as assessed by adenosine with and without pacing, respectively. Therefore, our study clearly demonstrates that N_2O, compared with N_2, has no direct effect on overall arteriolar coronary tone as indicated by its lack of additional effect on coronary flow with a constant coronary perfusion pressure. We also found that there was no significant difference in the release of degradation products of high-energy phosphates (*i.e.*, adenosine and inosine) when N_2O was substituted for N_2. If N_2O were to cause a redistribution of intramyocardial flow rather than a change in total flow, release of these products of ischemic metabolism might be greater with N_2O than with N_2.

Substitution of N_2O for N_2 produced no change in O_2 consumption or in the O_2 supply-to-demand ratio that, along with no change in coronary flow, suggests that intrinsic regulators of coronary flow were not altered. Moreover, the increase in coronary flow with N_2O was submaximal. As with N_2 alone, which was discussed above, this is indicated by the greater vasodilatation during arrest and pacing that occurred with intracoronary injection of adenosine. The lack of a change in the O_2 supply-to-demand ratio is reflected by the stable percentage extraction of O_2 with exposure either to N_2 or N_2O.

Several recent studies in dogs[23–27] suggested that, when N_2O is substituted for N_2 in acute preparations with a stenosed coronary artery, global and ischemic regional cardiac contractile indicators, such as LVP, its peak positive derivative, and segment shortening, are reduced. Because adjuvant opioids,[22,23,25] barbiturates,[22–24,26,27] or volatile anesthetics[23–27] were also administered, and because extracardiac factors could not be adequately controlled, the significance of the regional ischemic effects of administration of N_2O alone cannot be adequately ascertained. A recent acute dog study[28] suggested that N_2O can also impair return of regional myocardial function and increase mortality with reperfusion after ischemia. In dogs anesthetized with pentobarbital and given 70% N_2O for 15 min in place of 70% N_2 before total coronary occlusion, reperfusion was associated with a significantly greater depression of segment shortening up to 3 h after reperfusion and with a higher overall mortality than in control dogs given N_2.

In summary, our results demonstrate that 48% N_2O, when substituted for 48% N_2, has minimal direct effects in the isolated heart. Spontaneous atrial rate, AV conduction time, coronary flow, percentage O_2 extraction, and the O_2 supply-to-demand ratio are unchanged. When N_2 is substituted for N_2O, only a small but significant depression of two indices of contractility, peak isovolumetric pressure and its positive derivative, is observed. These results may not be surprising in that N_2O has a much lower anesthetic potency than any of the commonly used volatile anesthetics. When the effects of 48% N_2O (approximately 0.46 MAC for humans[18] and 0.35 MAC for rats[29]) are compared with the effects of 0.5% halothane, 1.1% enflurane, and 0.7% isoflurane (approximately 0.5 MAC for the guinea pig[30]) in isolated hearts,[31] N_2O appears much less depressant than these volatile agents on depressing HR, LVP, and coronary vascular tone. With development of more advanced noninvasive tests of cardiac function than those used previously, additional human studies would be useful in assessing the individual effects of N_2O without adjuvant drugs and other anesthetics.

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References

1. Kawamura R, Stanley TH, English JB, Hill GE, Liu W-S, Webster LR: Cardiovascular responses to nitrous oxide exposure for two hours in man. Anesth Analg 59:93–99, 1980
2. Eisele JH, Smith NT: Cardiovascular effects of 40 percent nitrous oxide in man. Anesth Analg 51:956–963, 1972
3. Eriksen S, Johannsen G, Frost N: Effects of nitrous oxide on systolic time intervals. Acta Anaesthesiol Scand 24:74–78, 1980
4. Lichtenthal P, Philip J, Sloss LJ, Gabel R, Lesch M: Administration of nitrous oxide in normal subjects. Chest 72:316–322, 1977
5. Goldberg AH, Sohn YZ, Phear WPC: Direct myocardial effects of nitrous oxide. ANESTHESIOLOGY 37:373–380, 1972
6. Lawson D, Frazer M, Lynch III C: Is nitrous oxide a myocardial depressant? A reexamination *in vitro* (abstract). ANESTHESIOLOGY 71:A503, 1989
7. Motomura S, Kissin I, Aultman DF, Reves JG: Effects of fentanyl and nitrous oxide on contractility of blood-perfused papillary muscle of the dog. Anesth Analg 63:47–50, 1984
8. Thorburn J, Smith G, Vance JP, Brown DM: Effect of nitrous oxide on the cardiovascular system and coronary circulation of the dog. Br J Anaesth 51:937–942, 1979
9. Lundborg RO, Milde JH, Theye RA: Effect of nitrous oxide on myocardial contractility of dogs. Can Anaesth Soc J 13:361–367, 1966
10. Price HL: Myocardial depression by nitrous oxide and its reversal by Ca^{++}. ANESTHESIOLOGY 44:211–215, 1976
11. Buljubasic N, Marijic J, Stowe, DF, Kampine JP, Bosnjak ZJ: Antidysrhythmic effects of halothane during ischemia: Correlation with changes in anaerobic glycolysis (abstract). Physiologist 33: A39, 1990
12. Marijic J, Stowe DF, Turner LA, Kampine JP, Bosnjak ZJ: Differential protective effects of halothane and isoflurane against hypoxic and reoxygenation injury in the isolated guinea pig heart. ANESTHESIOLOGY 73:976–983, 1990
13. Stowe DF: Vasodilator responses to moderate hypoxia after submaximal adenosine injection or coronary occlusion in isolated perfused guinea pig hearts. Circ Res 47:392–399, 1980
14. Jones DP: Intracellular diffusion gradients of O_2 and ATP. Am J Physiol 250:C663–C675, 1986
15. Bittl JA, Ingwall JS: Reaction rates of creatine kinase and ATP synthesis in the isolated heart. J Biol Chem 260:3512–3517, 1985
16. Katz LW, Swain JA, Portman MA, Balaban RS: Relation between phosphate metabolites and oxygen consumption of heart *in vivo*. Am J Physiol 256:H265–H274, 1989
17. Russell GB, Snider MT, Richard RB, Loomis JL: Hyperbaric nitrous oxide as a sole anesthetic agent in humans. Anesth Analg 70:289–295, 1990
18. Hornbein TF, Eger EI II, Winter PM, Smith G, Wetstone D, Smith KH: The minimum alveolar concentration of nitrous oxide in man. Anesth Analg 61:553–556, 1982
19. Ebert TJ: Differential effects of nitrous oxide on baroreflex control of heart rate and peripheral sympathetic nerve activity in humans. ANESTHESIOLOGY 72:16–22, 1990
20. Roizen MF, Plummer GO, Lichtor JL: Nitrous oxide and dysrhythmias. ANESTHESIOLOGY 66:427–431, 1987
21. Dottori O, Haggendal E, Linder E, Nordstrom G, Seeman T: The haemodynamic effects of nitrous oxide anaesthesia on myocardial blood flow in dogs. Acta Anaesthesiol Scand 20:421–428, 1976
22. Wilkowski DAW, Sill JC, Bonta W, Owen R, Bove AA: Nitrous oxide constricts epicardial coronary arteries without effect on coronary arterioles. ANESTHESIOLOGY 66:659–665, 1987
23. Philbin D, Foex P, Drummond G, Lowenstein E, Ryder WA, Jones LA: Postsystolic shortening of canine left ventricle supplied by a stenotic coronary artery when nitrous oxide is added in the presence of narcotics. ANESTHESIOLOGY 62:166–174, 1985
24. Ramsay JG, Arvieux CC, Foex P, Philbin DM, Jeavons P, Ryder WA, Jones LA: Regional and global myocardial function in the dog when nitrous oxide is added to halothane in the presence of critical coronary artery constriction. Anesth Analg 65:431–436, 1986
25. Leone BJ, Philbin DM, Lehot JJ, Foex P, Ryder WA: Gradual or abrupt nitrous oxide administration in a canine model of critical coronary stenosis induces regional myocardial dysfunction that is worsened by halothane. Anesth Analg 67:814–822, 1988
26. Nathan HJ: Nitrous oxide worsens myocardial ischemia in isoflurane-anesthetized dogs. ANESTHESIOLOGY 68:407–415, 1988
27. Nathan HJ: Control of hemodynamics prevents worsening of myocardial ischemia when nitrous oxide is administered to isoflurane-anesthetized dogs. ANESTHESIOLOGY 71:686–694, 1989
28. Siker D, Pelc LR, Kampine JP, Schmeling WT, Warltier DC: Nitrous oxide depresses functional recovery of stunned myocardium in dogs (abstract). ANESTHESIOLOGY 71:A476, 1989
29. Difazio CA, Brown RE, Ball CG, Heckel CG, Kennedy SS: Additive effects of anesthetics and theories of anesthesia. ANESTHESIOLOGY 36:57–63, 1972
30. Seifen AB, Kennedy RH, Bray JP, Seifen E: Estimation of minimum alveolar concentration (MAC) for halothane, enflurane and isoflurane in spontaneously breathing guinea pigs. Lab Anim Sci 39:579–581, 1989
31. Marijic J, Bosnjak ZJ, Stowe DF, Kampine JP: Effects and interaction of verapamil and volatile anesthetics on the isolated perfused guinea pig heart. ANESTHESIOLOGY 69:914–922, 1988