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Myocardial Performance and N_2O Analgesia in Coronary-artery Disease

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Inhalation of 40 per cent N_2O by nine patients who had occlusive disease in two or more coronary arteries with elevation of left ventricular end-diastolic pressures (LVEDP) significantly decreased arterial pressure (average 5 per cent) and myocardial contractility as measured by dP/dt/CPIP (average 14 per cent), and increased LVEDP (average 21 per cent). N_2O had no significant effect in four patients who had angina without angiographically demonstrable coronary arterial disease. It is concluded that N_2O depresses myocardial function in patients who have occlusion of the coronary arteries and impaired left ventricular function. (Key words: Anesthetics, gases, nitrous oxide; Heart, contractility, nitrous oxide; Heart, coronary artery disease.)

THE CARDIAC EFFECT in man of N_2O given in analgesic concentrations is unclear. The few published hemodynamic studies of N_2O have been done under varying clinical circumstances. In one study administration of 40 per cent N_2O to awake healthy young volunteers depressed ventricular function approximately 5 per cent after 10 minutes, 8 per cent after 20 minutes, and 15 per cent after 30 minutes, while cardiac output decreased 11, 13, and 19 per cent, respectively.[1] On the other hand, patients with myocardial infarction given 50 per cent N_2O for analgesia over 30 minutes showed no significant change in mean cardiac index, stroke index, heart rate, systemic or pulmonary arterial pressure, or systemic vascular resistance.[2] This apparent paradox, cardiac disease patients showing little effect of N_2O inhalation, may be explained either by the different methods employed or by the clinical settings, which could alter the responses. For example, the latter group had pain, which was usually relieved by N_2O. To clarify this issue, and to evaluate our clinical impression that N_2O depresses the circulation in coronary-artery bypass operations using N_2O–narcotic anesthesia, we investigated the effects of N_2O on the cardiovascular hemodynamics of patients suspected to have coronary-artery disease during cardiac catheterization at a time when they were not having angina.

Methods and Materials

Thirteen patients (ages 39 to 62 years) suspected to have coronary-artery disease, undergoing left heart catheterization and coronary angiography, were studied at the end of the routine catheterization procedure. The purpose and plan of the study were explained to each patient the prior evening. One hour before catheterization, each patient received 50 mg meperidine, im, for sedation. Our study started approximately 3–4 hours later. Both 40 per cent N_2 in O_2 and 40 per cent N_2O in O_2 were administered to each subject through a face mask for 10 minutes. This allowed each patient to serve as his own control. After the first few studies it was apparent that the left ventricular end-diastolic pressure (LVEDP) was elevated by the Hypaque dye and did not return to control levels for about 30 minutes.[3] Since LVEDP was declining during the time of study we chose to give N_2 in O_2 first, so that any change in LVEDP during N_2O in O_2 would be less likely to reflect a residual influence of the dye. After each ten-minute period, the following

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TABLE 1. Clinical Data*

	Age (Years), Sex	Past History of Myocardial Infarction	Ejection Fraction	LVEDP (mm Hg)	Coronary Vessels Occluded (70 Per Cent or More)	Left Ventricle Dyskinesis
Coronary-artery disease						
Patient 1	62, M	Yes 1	.31	13.0	2	Yes
Patient 2	56, M	No	.54	9.0	1	Yes
Patient 3	53, M	Yes 2	.30	8.0	1	No
Patient 4	61, M	Yes 1	.34	15.0	3	Yes
Patient 5	53, F	Yes 2	.57	5.0	3	No
Patient 6	57, M	Yes 1	.40	7.0	1	No
Patient 7	53, M	Yes 2	.59	15.0	3	Yes
Patient 8	58, M	Yes 1	.43	9.8	3	Yes
Patient 9	50, M	Yes 2	.49	8.0	2	Yes
AVERAGE	55.8	8/9	.44	9.9	—	6/9
No coronary-artery disease						
Patient 10	47, M	No	.50	1.0	None	No
Patient 11	47, M	?	—	10.0	None	No
Patient 12	53, F	No	—	1.0	None	No
Patient 13	39, M	No	.60	8.0	None	No
AVERAGE	46.5	—	.55	5.0	—	—

* Pertinent clinical data comparing patients with significant coronary artery disease (1–9) with those without coronary angiographic findings (10–13). Left ventricular dyskinesis is the inadequate contraction of part of the left ventricular wall in patients with histories of infarcted myocardium. Ejection fraction denotes that portion of left ventricular end-diastolic volume that is ejected out of the ventricle into the aorta with each heart beat. LVEDP (ventricular preload) is a measurement of intraventricular pressures just prior to systolic contraction of the ventricle.

phasic measurements were made: ECG, arterial pressure, and left ventricular pressure. In addition, duplicate dye-dilution cardiac output curves and arterial blood-gas analyses were performed. From these measurements, heart rate, mean arterial pressure, left ventricular end-diastolic pressure (LVEDP), cardiac index (C.I.), and rate of rise of ventricular pressure (dP/dt) were obtained. To minimize the effects of afterload, the dP/dt was taken at common peak isovolumic pressures (CPIP), and this ratio (dP/dt/CPIP) was used as an index of myocardial contractility.[4] At least ten heart beats were used for measurements in each analysis.

Results

Clinically the patients fell into two groups: those who had cardiac symptoms but no evidence of coronary-artery disease as determined by angiography (four patients), and those who had symptoms and definite coronary-artery lesions (nine patients). Table 1 shows that the latter group had a high incidence of prior myocardial infarction and left ventricular dyskinesis. They also had low ejection fractions and elevated LVEDP's. Patients 10–13, with no evidence of coronary-artery disease and normal hemodynamics, although not necessarily healthy, are compared with the patients who had demonstrated coronary-artery disease (Patients 1–9).

The experimental data are presented in table 2. In all patients with demonstrated coronary arterial occlusions N_2O depressed myocardial performance and increased left ventricular loading. Compared with N_2 in O_2, N_2O in O_2 produced an average decrease in left ventricular contractility (dP/dt/CPIP) of 13.6 per cent and an average rise in left ventricular end-diastolic pressure (LVEDP) of 21.3 per cent. Cardiac index (C.I.) decreased an average of 6.8 per cent, while mean arterial blood pressure fell only 4.9 per cent, indicating an increase in total calculated pe-

TABLE 2. Experimental

	Heart Rate (Beats/Min)			MAP (mm Hg)		
	N_2O_2	$N_2O\ O_2$	Per Cent Change	N_2O_2	$N_2O\ O_2$	Per Cent Change
Coronary-artery disease						
Patient 1	66	66	0	85	85	0
Patient 2	78	72	− 7.6	93	87	− 6.4
Patient 3	70	70	0	71	73	− 2.8
Patient 4	54	54	0	105	90	−14.2
Patient 5	84	84	0	96	102	+ 6.2
Patient 6	65	68	+ 4.6	74	67	− 9.4
Patient 7	76	62	−18.4	74	69	− 6.7
Patient 8	84	88	+ 4.7	94	86	− 8.5
Patient 9	60	56	− 6.6	77	75	− 2.6
AVERAGE	70.7	68.8	− 2.6	85.4	81.5	− 4.9
SEM	± 3.5	± 3.8	± 2.4	± 4.0	± 3.7	± 1.9
P			N.S.			<0.05
No coronary-artery disease						
Patient 10	92	88	− 4.3	81	81	0
Patient 11	72	78	+ 8.3	85	78	− 8.2
Patient 12	56	56	0	82	94	+14.6
Patient 13	60	60	0	100	102	+ 2.0
AVERAGE	70.0	70.5	+ 1.0	87.0	88.7	+ 2.1
SEM	± 8.0	± 7.5	± 2.6	± 4.4	± 5.6	± 4.7
P			N.S.			N.S.

* Changes in heart rate (HR), mean arterial pressure, cardiac index, rate of rise of left ventricular pressure (LVEDP) that occurred when N_2O was administered. The mean values ± 1 SEM of all variables vessel disease. Significances for a two-tailed Students' t test are indicated for the change between N_2 and N_2O.

† $P < 0.05$ for difference in percentage change between Patients 1–9 and Patients 10–13.

ripheral resistance. The average heart rate change was a decrease of only 2 beats/min. The changes in mean arterial pressure (MAP), left ventricular performance (dP/dt/CPIP) and end-diastolic pressure (LVEDP) when N_2O replaced N_2 were significant in the patients who had coronary-artery disease.

In contrast, among the patients free of demonstrable coronary-artery disease, N_2O produced insignificant changes: dP/dt/CPIP, −5.1 per cent; LVEDP, +15.4 per cent; cardiac index, −0.6 per cent; arterial pressure, +2.1 per cent; heart rate, +0.5 beats/min. When the data was normalized for large individual differences, the only statistically significant difference between the two groups was the decrease in dP/dt/CPIP, which was greater following N_2O in the coronary-artery-disease group. Of the nine patients who had coronary-artery disease, six had impairment in left ventricular contractile pattern (dyskinesis, hypokinesis, akinesis), and these patients had the largest decreases in dP/dt/CPIP and cardiac index (C.I.) during N_2O inhalation.

Blood-gas analysis showed no significant difference in these variables between N_2 and N_2O administrations or between the two patient groups.

None of the patients lost consciousness during exposure to N_2O. Several experienced dizziness, and most related a feeling of light intoxication.

Discussion

A decreasing left ventricular dP/dt/CPIP in the face of a rising LVEDP suggests a failing heart. This response to N_2O was observed when N_2O was added to morphine or fentanyl anesthesia,[5,6] but not when added to inhalation agents.[7–9] These responses, however, may represent a drug interaction that would not be present in awake subjects. It is possible that the myocardial status of the patients in

Data*

Cardiac Index (l/Min/m²)			dP/dt CPIP (mm Hg/Sec)			LVEDP (mm Hg)		
N_2O_2	$N_2O O_2$	Per Cent Change	N_2O_2	$N_2O O_2$	Per Cent Change	N_2O_2	$N_2O O_2$	Per Cent Change
2.58	2.39	− 7.3	35.4	32.0	− 9.6	12.7	16.4	+29
3.36	1.92	−42.8	28.6	24.8	−13.2	11.3	12.4	+ 9.7
1.65	1.82	+10.3	27.8	24.7	−11.1	12.0	14.4	+20
2.23	2.00	−10.3	39.8	30.0	−24.6	15.0	16.0	+ 6.6
2.98	2.80	− 6.0	23.6	20.8	−11.8	5.0	6.5	+30
2.62	2.64	+ 0.7	62.8	60.5	− 3.6	5.5	6.5	+18
2.28	2.20	− 3.5	21.7	16.8	−22.5	4.6	7.7	+67
2.76	2.98	+ 7.9	32.0	28.8	−10.0	9.8	10.1	+ 3.0
2.80	2.53	− 9.6	28.8	24.3	−15.6	15.2	16.6	+ 9.2
2.58	2.36	− 6.8	33.3	29.1	−13.6	10.1	11.8	+21.3
± .16	± .13	± 5.1	± 4.1	± 4.2	± 2.1	± 1.4	± 1.4	± 6.5
		N.S.			<0.001†			<0.05
3.03	2.83	− 6.6	30.2	28.0	− 7.3	0.9	1.0	+11.1
3.04	3.69	+21.3	39.2	34.4	−12.3	10.8	11.5	+ 6.4
2.13	2.11	− 0.9	46.3	44.8	− 3.2	0.8	1.1	+37.5
3.00	2.51	−16.3	36.0	37.0	+ 2.7	13.4	14.3	+ 6.7
2.80	2.78	− 0.6	37.9	36.0	− 5.1	6.47	6.97	+15.4
± .22	± .33	± 7.9	± 3.3	± 3.4	± 3.2	± 3.2	± 3.4	± 7.4
		N.S.			N.S.			N.S.

pressure measured at a common isovolumic pressure (dP/dt/CPIP), and left ventricular end-diastolic are shown for the two groups of patients: 1–9, with coronary-artery disease; and 10–13, free of coronary

the present study was more vulnerable to any depressant agent or drug because of the preceding dye injection, which temporarily increases the preload.[3] It is impossible to evaluate this potential influence, however.

The results of the present study are more in keeping with the results of N_2O in non-anesthetized healthy subjects, in that left ventricular function was depressed and there was an increase in total peripheral resistance.[1] Our patients with coronary-artery disease had a decrease in dP/dt/CPIP of 13.6 per cent, in contrast to the reaction in the patients with angina without demonstrable coronary-artery occlusion, in whom dP/dt/CPIP fell 5.1 per cent. The latter is comparable to the 5 per cent decrease in myocardial contractility (ballistocardiogram) after 10 minutes of 40 per cent N_2O among healthy non-anesthetized volunteers.[1]

In a study similar to the present one, Thornton *et al.*[10] evaluated the effects of 50 per cent N_2O administered for 10 minutes to patients who had a variety of cardiac abnormalities. The study was also performed during cardiac catheterization, and N_2 was given in a manner similar to N_2O for comparison. Cardiac output decreased 12.0 per cent during exposure to N_2O and only 4.6 per cent during N_2; the difference, however, was statistically insignificant. The LVEDP did rise significantly in response to both N_2O in O_2 and N_2 in O_2, suggesting some sympathetic response to either the procedure or the 50 per cent O_2. Evaluation of ventricular function *per se* was not mentioned.

The difference between our results and those of Kerr *et al.*,[2] who administered N_2O to patients with myocardial infarcts for analgesia, may be a consequence of the procedure, in which sick patients were asked to breathe room air for 30 minutes through a face mask, after which a gas mixture of N_2O in O_2 (50/50) was started. Since these patients were in pain,

it is likely that there was considerable sympathetic stimulation, which may not have been eliminated by the analgesia provided by N_2O. That cardiac index, stroke index, arterial pressure, and systemic vascular resistance were relatively unchanged when the inhaled gas was changed from air to N_2O in O_2 could be due to the improved arterial oxygenation, as the mean Pa_{O_2} rose from 63 to 95 mm Hg. In a damaged heart, an improvement in oxygen tension of this magnitude could be critical, and since the effects of 50 per cent O_2 plus N_2 were not assessed for comparison, it may be misleading to consider N_2O harmless under these circumstances.

The present study raises the question of the validity of myocardial contractility measurements in patients with coronary-artery disease, especially those with demonstrated left ventricular dyskinesis. Few studies have assessed the effects of drugs on myocardial performance in coronary-artery disease patients. Parmley,[11,12] in a clinical study of patients who had acute myocardial infarction, found LV dP/dt measurements better than contractile-element velocity calculations, but not as good as ventricular function curves, in separating non-survivors from survivors. Apparently the LV dP/dt reflects only the normally contracting myocardial units, so that nonfunctioning areas make little or no difference in the measurements of muscle-shortening velocity.[13] That a number of contractile units have been lost due to infarction accounts for the fact that myocardial pump function may be significantly depressed in these patients.

In the present study, N_2O depressed both pump performance (C.I.) and contractility (dP/dt/CPIP) in almost all patients. Those with demonstrable coronary-artery disease were more depressed by N_2O. Indeed, it has been shown that cardiac patients do not tolerate N_2O well during balanced anesthesia with narcotics,[5,6] and the authors' clinical experience (unpublished data) suggests that in similar patients, the extent of cardiac depression can be directly correlated with the concentration of N_2O employed. Mild depression of the ischemic heart is accepted, and in some clinical circumstances may be beneficial when the depressant drug reduces myocardial oxygen consumption at the same time. Unfortunately, we do not know the precise effect of N_2O on myocardial work, particularly in the ischemic heart. The small changes in cardiac index and systolic blood pressure in this study indicate minimal reduction in stroke work during N_2O inhalation compared with the decrease in contractility.

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