Anesthesiology
67:952–959, 1987

Effects of Nitrous Oxide on Coronary Perfusion after Coronary Air Embolism

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Coronary air embolism (CAE) can occur after heart surgery whenever air is present in the left heart or proximal aorta. When CAE occurs, its sequelae can range from electrocardiographic changes of ischemia to severe myocardial dysfunction and cardiac arrest. Since N_2O has been shown to have detrimental effects in the presence of coronary obstructions, as well as the tendency to enlarge air emboli, the authors tested the hypotheses that N_2O would enhance the deleterious effects of CAE, and that discontinuing N_2O at the time of CAE would minimize those effects. The effects of ventilation with and without N_2O on the cardiac insult due to left anterior descending CAE (0.02 ml · kg^{-1}) were studied in 27 swine. Global cardiovascular changes that occurred after CAE included decreases in cardiac output, systemic arterial and coronary perfusion pressure, and LV dP/dt, as well as increases in LVEDP. These parameters returned towards baseline over time when N_2O was discontinued at the time of CAE. Maintenance of N_2O in the inspired gas after CAE occurred was uniformly fatal within 2–4 min in this model. Regional myocardial ischemia was significantly greater in animals receiving N_2O, as documented by: 1) a greater incidence of elevations of epicardial ST-segments exceeding 3 mm from baseline in embolized and non-embolized coronary artery distributions, 2) a greater incidence of dysrhythmias (greater than 6 PVCs · min^{-1}), 3) longer duration of depression of coronary blood flow, 4) longer duration of post-ischemic coronary hyperemia, and 5) larger decreases with less recovery over time of regional myocardial lactate extraction. The authors conclude that N_2O should not be used following cardiopulmonary bypass, since even discontinuing it at the time of CAE is not sufficient to eliminate its deleterious effects. (Key words: Anesthetics, gases: nitrous oxide. Complications: myocardial dysfunction. Embolism: air; coronary.)

CORONARY AIR EMBOLISM is a well-known major complication of coronary revascularization and open heart surgery.[1–3] Its incidence is probably greater than generally recognized.[4] Air can enter the coronary arterial circulation any time the left side of the heart or proximal aorta is open to the atmosphere; this includes entry after aortotomies for proximal coronary grafting, during valve replacement, and after aortic cannulation for institution of cardiopulmonary bypass. Air emboli may enter the coronary circulation from the cardioplegic perfusate or from the cardiopulmonary bypass apparatus itself.

It is generally agreed that even small amounts of air in the left side of the heart and coronary arteries can embarrass cardiac function. As little as 0.05 milliliter of air in the left coronary artery can cause definite myocardial ischemia and infarction, cardiac arrest, ventricular dysrhythmias, including ventricular fibrillation, and a low cardiac output syndrome.[5] Prevention and treatment of this problem are, therefore, clinically important.[1,6,7] Currently recommended measures for prevention of coronary air embolism include ventricular venting, aspiration and venting of the ascending aorta, induced fibrillation, retrograde coronary perfusion, ventilation of the lungs to evacuate pulmonary venous air and subsequent removal of air from the left atrium after valve surgery, venting of coronary grafts through small needle holes, and routine use of arterial bubble detectors and in-line microfilters during cardiopulmonary bypass. All of these measures tend to minimize, but not eliminate, coronary air embolism. Once coronary air embolism has occurred, the severity of sequelae depends on the amount of air in the coronary system and the efficacy of treatment.

Nitrous oxide has been shown to cause global, as well as regional, myocardial dysfunction in both humans and laboratory animals with lesions that limit coronary blood flow. This occurs when it is used alone[8] or added to narcotics.[9,10] Regional wall dysfunction suggestive of ischemia associated with elevations in left ventricular end diastolic pressure, as well as decreases in systemic blood pressure, left ventricular dP/dt, and cardiac output, have been noted. Because of these potentially deleterious effects, when coronary air embolism is present, the use of nitrous oxide may further worsen cardiac dysfunction or ischemia. An additional problem with N_2O is that, because of its greater blood solubility than nitrogen, it can diffuse into an air embolus and cause it to expand, worsening the effects of coronary air embolism.

This study was performed to examine the cardiac effects of coronary air embolism in the presence and absence of ventilation with nitrous oxide in swine. We also tested the hypothesis that discontinuing nitrous oxide at the time of coronary air embolism would improve car-

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Received from the Department of Anesthesiology, Division of Cardiovascular Anesthesia, Rush-Presbyterian St. Luke's Medical Center, 1753 West Congress Parkway, Chicago, Illinois 60612. Accepted for publication July 22, 1987. Presented in part at the annual meeting of the International Anesthesia Research Society, March 17, 1987.
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TABLE 1. Protocol

Group	N	Preembolus		Embolus Type	Postembolus	
		Ventilation	FI_{O_2}		Ventilation	FI_{O_2}
I	6	Air/O_2	0.33	Air	O_2	1.0
II	6	N_2O/O_2	0.33	Air	O_2	1.0
III*	6	N_2O/O_2	0.33	Air	O_2	1.0
IV	6	N_2O/O_2	0.33	N_2O/Air (2:1)	O_2	1.0
V	3	N_2O/O_2	0.33	Air	N_2O/O_2	0.33

* Group III received an infusion of phenylephrine (see text).

diac performance and lessen the cardiovascular insult otherwise seen.

Materials and Methods

After approval by the Institutional Animal Care Committee, 27 Hampton-Landrace swine (23 ± 7 kg) were fasted overnight and then anesthetized with ketamine (25 $mg \cdot kg^{-1}$ im), positioned supine, and mechanically ventilated (Elema 900C servo-ventilator, Seimens-Elema, Solna, Sweden) *via* a cuffed endotracheal tube. After neuromuscular blockade was achieved and maintained with pancuronium, ventilation was adjusted to maintain a Pa_{CO_2} of 40 ± 5 mmHg. A thermister-tipped Swan-Ganz catheter (model 93A131-7F, Edwards Laboratories, Santa Anna, CA) was inserted *via* the right internal jugular vein and positioned by means of pressure monitoring into a branch of the pulmonary artery. A polyethylene catheter (2.5 mm internal diameter) was placed in the abdominal aorta *via* the right femoral artery for systemic blood pressure measurements and arterial blood sampling. The left femoral vein was cannulated for infusion of lactated ringers solution at 4 $ml \cdot kg^{-1} \cdot hr^{-1}$ throughout the experiment.

A midline thoracotomy was performed, the pericardial sac opened and a 0.023-mm(ID) polyethylene catheter placed through the ventricular apex into the left ventricular cavity to allow electronic differentiation of the first derivative of the left intraventricular pressure (LV dP/dt), as well as direct measurement of the left ventricular end diastolic pressure. The aortic root was dissected free of its fat pad, and aortic flow was measured by placing an appropriate sized electromagnetic flow probe (Gould SP7515; 16 or 18 mm) around the aortic root and connecting it to a Gould model 2201 blood flowmeter. Two sets of epicardial electrocardiogram leads were placed; one in the distribution of the left anterior descending coronary artery, and another in the distribution of the circumflex coronary artery. The left anterior descending coronary artery just distal to its first diagonal branch was dissected with care off the epicardium and encircled with an electromagnetic flow probe (Gould SP7517, 2–2.5 mm) to measure coronary artery blood flow (LAD-CBF). A 27-gauge needle, previously flushed with heparinized saline, was inserted into the left anterior descending coronary artery just proximal to the flow probe (after the first diagonal branch).

Temperature was monitored *via* the thermister probe of the Swan-Ganz catheter and was maintained at 37° C by surface heating and warmed intravenous fluids. Pulmonary and systemic vascular pressures were measured using Gould transducers (Model P23ID, Gould Instruments, Oxnard, CA). Recordings were made on an eight channel polygraph (Model 200, Gould Instruments, Cleveland, OH) and read at end-expiration. Arterial *p*H, P_{CO_2}, P_{O_2}, and hemoglobin were measured twice hourly by an automated analyzer (*p*H blood gas analyzer, Model 1301, and cooximeter Model 282, Instrumentation Laboratory, Lexington, MA) and the ventilator adjusted when necessary. Anesthesia was maintained with pentobarbital (20 $mg \cdot kg^{-1}$ iv administered just prior to thoracotomy and 15 $mg \cdot kg^{-1}$ iv after all surgical manipulation complete).

The animals were then divided into five groups (table 1). During the initial phase of the experiment, groups II, III, IV (N = 6 each), and V (N = 3) were ventilated with N_2O: O_2 (FI_{O_2} = 0.33) and group I (N = 6) with air: O_2 (FI_{O_2} = 0.33). Thirty minutes after the last dose of pentobarbital and stabilization of systemic and coronary blood flows occurred, baseline values of systemic mean arterial pressure (MAP), systemic diastolic arterial pressure (DBP), left ventricular end-diastolic pressure (LVEDP), left ventricular dP/dt, cardiac output (CO), heart rate (HR), blood flow in the left anterior descending coronary artery (LAD-CBF), epicardial ST segment elevations greater than 3 mm above baseline in the above coronary distributions, the number of premature ventricular contractions per minute, and coronary venous lactate levels sampled from the coronary vein draining the distribution of the LAD (using a 24-gauge angiocath) and systemic arterial lactate were obtained. Regional myocardial lactate extraction (RMLE) from the LAD distribution was calculated as the arterial-cor-

TABLE 2. Hemodynamic Responses to Coronary Air Embolism

Group	Time after CAE (Minutes)				
	−2	1	2	3	4
MAP (mmHg)					
I	110 ± 3	96 ± 8	109 ± 6	109 ± 5	109 ± 2
II*	87 ± 5	76 ± 5	76 ± 4	78 ± 5	78 ± 5
III	115 ± 2	96 ± 10	102 ± 7	112 ± 3	112 ± 3
IV*	93 ± 9	86 ± 8	86 ± 8	88 ± 10	89 ± 10
V	90 ± 11	78 ± 13	45 ± 7		
DBP (mmHg)					
I	96 ± 5	86 ± 7	97 ± 7	94 ± 5	94 ± 3
II†	71 ± 3	61 ± 6	62 ± 7	64 ± 6	65 ± 5
III	93 ± 1	87 ± 7	93 ± 5	88 ± 2	90 ± 2
IV	78 ± 8	72 ± 8	71 ± 9	73 ± 10	74 ± 10
V	68 ± 10	58 ± 10	33 ± 7		
LVEDP (mmHg)					
I	1.8 ± 0.5	3.3 ± 0.9	3.9 ± 0.8	2.9 ± 1.1	2.5 ± 1.4
II	3.8 ± 0.9	4.2 ± 1.2	4.2 ± 1.3	4.6 ± 1.3	4.3 ± 1.1
III	5.4 ± 0.5	6.3 ± 0.9	7.5 ± 1.4	7.9 ± 2.7	4.6 ± 1.1
IV	4.6 ± 1.5	4.2 ± 1.9	4.6 ± 2.4	5.4 ± 2.2	6.3 ± 3.0
V	1.7 ± 1.5	4.0 ± 1.7	4.3 ± 2.8		
CPP (mmHg)					
I	94 ± 3	83 ± 6	93 ± 7	91 ± 6	92 ± 3
II‡	67 ± 5	57 ± 5	58 ± 6	60 ± 5	60 ± 5
III	88 ± 1	81 ± 7	85 ± 6	80 ± 4	85 ± 2
IV‡	74 ± 8	68 ± 8	66 ± 9	68 ± 9	67 ± 9
V	66 ± 10	54 ± 11	30 ± 8		
LV dP/dt (mmHg/sec)					
I§	1225 ± 83	1000 ± 111	1142 ± 90	1175 ± 88	1191 ± 83
II	925 ± 54	791 ± 47	833 ± 44	850 ± 40	875 ± 44
III	942 ± 41	758 ± 105	825 ± 97	925 ± 77	958 ± 60
IV	900 ± 98	833 ± 99	908 ± 103	950 ± 108	966 ± 117
V	1227 ± 92	893 ± 115	640 ± 108		
CO (ml/min)					
I	2283 ± 111	2000 ± 120	2050 ± 159	2117 ± 177	2150 ± 146
II	2300 ± 144	2000 ± 139	2050 ± 138	2133 ± 152	2067 ± 174
III	2283 ± 158	1800 ± 140	1917 ± 125	1933 ± 99	2033 ± 88
IV	2167 ± 273	1933 ± 215	1950 ± 220	1950 ± 292	1917 ± 297
V	1985 ± 126	1565 ± 152	1000 ± 350		
HR (bpm)					
I	115 ± 4	116 ± 3	116 ± 3	115 ± 2	115 ± 3
II	110 ± 6	111 ± 6	112 ± 6	111 ± 6	113 ± 6
III††	84 ± 5	87 ± 4	88 ± 4	84 ± 4	82 ± 4
IV	104 ± 17	102 ± 17	99 ± 16	99 ± 16	96 ± 15
V	101 ± 13	94 ± 14	55 ± 7		

Values are means ± standard deviation. Group V data presented to demonstrate similar baseline values; group V not included in statistical analysis.

* Denotes group II and IV significantly less than I and III at all times ($P < 0.05$).

† Denotes group II significantly less than I and III at all times ($P < 0.05$).

‡ Denotes group II and IV significantly less than I and III at all times ($P < 0.05$).

§ Denotes group I significantly greater than II, III, and IV at all times ($P < 0.05$).

¶ Denotes group II significantly greater than III at 10 min ($P < 0.05$).

** Denotes group II significantly greater than I, III, and IV at these times ($P < 0.05$).

†† Denotes group III significantly less than I, II, and IV at all times ($P < 0.5$).

onary vein lactate difference divided by arterial lactate content. Coronary perfusion pressure was calculated as the difference between systemic diastolic blood pressure and left ventricular end diastolic pressure.

Group III animals received an infusion of phenylephrine titrated to produce systemic diastolic arterial pressure (95 ± 8 mmHg) similar to group I (not receiving N_2O). After baseline measurements, the inspired gas mixture was changed to 100% O_2 in groups I through IV and, simultaneously, a 0.02 ml · kg^{-1} of body weight gas embolus was injected directly into the LAD coronary artery just distal to the flow probe (after the first

TABLE 2. *continued*

Time after CAE (Minutes)					
5	10	15	20	30	45
108 ± 5	109 ± 3	111 ± 3	110 ± 3	113 ± 4	120 ± 6
80 ± 3	89 ± 4	92 ± 4	96 ± 5	100 ± 4	105 ± 7
115 ± 3	121 ± 4	123 ± 4	125 ± 4	120 ± 7	123 ± 5
90 ± 10	95 ± 11	101 ± 12	101 ± 11	105 ± 12	107 ± 11
93 ± 3	93 ± 4	95 ± 4	95 ± 5	97 ± 5	100 ± 7
66 ± 5	73 ± 4	77 ± 4	79 ± 4	81 ± 5	87 ± 5
92 ± 4	98 ± 4	101 ± 4	103 ± 3	98 ± 6	102 ± 5
74 ± 11	80 ± 11	84 ± 12	86 ± 10	88 ± 12	89 ± 11
1.7 ± 0.9	2.9 ± 1.4	2.1 ± 1.1	2.0 ± 0.8	1.6 ± 0.5	1.3 ± 0.6
4.2 ± 1.0	4.2 ± 0.6	3.3 ± 1.1	2.9 ± 0.5	2.3 ± 0.8	2.0 ± 0.8
4.5 ± 0.8	5.0 ± 1.5	4.8 ± 0 9	4.2 ± 0.9	4.2 ± 0.9	3.9 ± 1.0
5.2 ± 2.2	4.8 ± 1.4	4.3 ± 1.0	5.4 ± 0.8	5.0 ± 1.0	4.2 ± 0.9
92 ± 5	90 ± 3	93 ± 4	93 ± 4	95 ± 5	98 ± 5
61 ± 3	69 ± 4	73 ± 4	76 ± 4	79 ± 5	84 ± 7
87 ± 4	93 ± 4	97 ± 3	98 ± 3	93 ± 6	98 ± 5
69 ± 11	75 ± 10	79 ± 11	80 ± 10	83 ± 12	85 ± 11
1166 ± 91	1150 ± 111	1167 ± 116	1175 ± 116	1167 ± 127	1140 ± 117
892 ± 47	1000 ± 45	958 ± 33	1016 ± 50	1066 ± 52	960 ± 48
983 ± 46	1025 ± 18	1050 ± 47	1066 ± 67	1066 ± 73	1050 ± 49
975 ± 105	1025 ± 112	1066 ± 110	1092 ± 111	1100 ± 111	1025 ± 106
2117 ± 122	2133 ± 122	2117 ± 195	2033 ± 215	1933 ± 238	1900 ± 188
2067 ± 174	2333 ± 115¶	2450 ± 128**	2483 ± 140**	2417 ± 121**	2367 ± 169**
2017 ± 66	1933 ± 43	1900 ± 69	1917 ± 72	1883 ± 104	1867 ± 115
1933 ± 285	2033 ± 231	2050 ± 208	2067 ± 178	1967 ± 193	1850 ± 167
115 ± 3	115 ± 3	113 ± 3	110 ± 3	107 ± 4	110 ± 3
113 ± 6	112 ± 6	112 ± 6	112 ± 5	115 ± 6	114 ± 5
82 ± 4	79 ± 4	79 ± 4	79 ± 6	82 ± 4	80 ± 5
97 ± 14	98 ± 14	98 ± 15	101 ± 15	106 ± 16	96 ± 7

diagonal branch) using the previously inserted 27-gauge needle. Group V did not have the inspired gas mixture changed, and remained ventilated with N_2O:O_2 (2:1) both during and after the coronary embolus was given. Groups I, II, III, and V received an air embolus, while group IV received an embolus of N_2O:air (2:1). The above physiologic measurements were repeated at 1, 2, 3, 4, 5, 10, 15, 20, 30, and 45 min after embolus. The length of time after embolus until a return of coronary artery blood flow to baseline before post-ischemic hyperemia ensued (time to hyperemia) was noted. Additionally, the time until return to base-

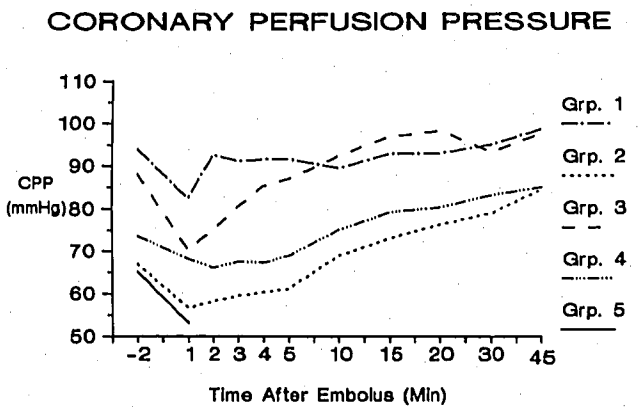

FIG. 1. Effects of coronary embolism on coronary perfusion pressure under various conditions (see text). Group 2 and 4 < 1 and 3 at all times ($P < 0.05$).

line coronary artery blood flow post-hyperemia was noted (duration of hyperemia). Preembolic baseline regional myocardial lactate extractions were determined, as well as at 5 and 15 min post-embolus.

Physiologic data were compared using multiple analysis of variance (MANOVA) with repeated measures in one variable. Times to hyperemia and duration of hyperemia were analyzed using a one-way analysis of variance (ANOVA). *Post hoc* tests were performed when appropriate using the Tukey-a method. ECG data was analyzed using chi-square analysis. A probability level of less than 0.05 ($P < 0.05$) was considered statistically significant.

Results

Prior to coronary air embolism, there were no significant differences in body weight, cardiac output,

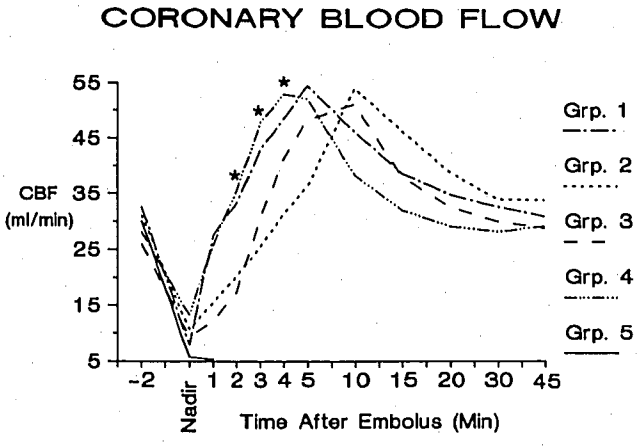

FIG. 2. Effects of coronary embolism on LAD coronary blood flow under various conditions (see text). Group 1 and 4 > 2 at noted times ($P < 0.05$).

LVEDP, or LAD coronary artery blood flow among the groups. Nitrous oxide lowered systemic mean and diastolic arterial pressures (without significantly depressing the healthy myocardium), and hence decreased coronary perfusion pressures in groups II and IV compared to group I, which was not exposed to N_2O (table 2; fig. 1). This trend between groups was present at all times during the experiment, and was the impetus to study a group of animals exposed to N_2O, which had coronary perfusion pressure increased by continuous careful titration of a phenylephrine infusion to mimic that in group I (group III, fig. 1). Baseline LV dP/dt was slightly higher in group I than in other groups, probably due to mild myocardial depression by N_2O in groups II–IV. Pre-embolus, there was no electrocardiographic evidence for myocardial ischemia, nor any ventricular ectopy in any groups.

After coronary embolization, coronary artery blood flow fell to similar nadirs in less than 15 s in all groups (fig. 2). The subsequent myocardial ischemia was accompanied by a rapid fall in MAP, DBP, CPP, CO, and LV dP/dt in all groups. This was most profound in group V animals, all of which expired within 1–4 min of coronary embolization when N_2O remained in the inspired gas mixture. This limb of the experimental protocol was terminated at N = 3 for this reason (see Discussion). There was a gradual recovery of MAP, DBP, CPP, CO, and LV dP/dt over 5 min in groups I–IV. However, cardiac output remained slightly depressed compared to baseline levels even 15–45 min after embolus in groups I, III, and IV. Group II animals had cardiac outputs that were significantly greater than the other groups at these times, despite similar conditions of LVEDP, HR, and LV dP/dt. The reasons for the difference in cardiac output of approximately 400 ml/min are unclear, but may be due to a decreased afterload (lower systemic vascular resistance) in group II compared to the other groups at these times. LVEDP rose initially and recovered gradually toward baseline values over 10 min.

LAD coronary artery blood flow followed a similar pattern in all groups, but the time course of this pattern was different among groups (fig. 3). Groups I–IV all had an initial recovery of LAD-CBF to baseline perfusion followed by a period of post-ischemic reactive hyperemia. Groups I and IV had rapid reestablishment of LAD-CBF (1.6 ± 0.9 and 1.4 ± 0.6 min) and recovery from hyperemia (15.8 ± 4.0 and 11.3 ± 1.2 min, respectively) following coronary embolization. Groups II and III did not reestablish baseline perfusion until 4.3 ± 2.0 and 3.0 ± 0.6 min post-embolus, and did not recover from hyperemia until 23.8 ± 3.5 and 21.3 ± 1.9 min, respectively. These times represent a statistically significantly longer period of coronary flow depression in

group II and statistically longer duration of hyperemia in groups II and III compared to groups I and IV. Group IV also had a statistically shorter period of hyperemia than group I ($P < 0.05$).

Five minutes after coronary embolization, regional myocardial lactate extraction (RMLE) decreased in all groups. The greatest decrease occurred in group II, and this was similar to that noted in group III. Group I (no N_2O) and group IV (nitrous gaseous embolus with N_2O in inspired gas mixture) both had similar but smaller decreases in RMLE compared to groups II and III. At 15 min post-embolus, RMLE had returned nearly to baseline values in all groups except in group II, which demonstrated the least recovery towards baseline values of all the groups (table 3).

Electrocardiographic evidence of ischemia was quantitated by measuring the incidence of greater than 3-mm ST segment elevation from baseline in the epicardial regions of the embolized vessel (LAD distribution), as well as in adjacent but non-embolized tissue (circumflex distribution). There was a significantly greater incidence of ischemic changes in the distribution of LAD perfusion in groups II and III in the first 5 min post-embolus than groups I and IV (table 4, $P < 0.02$). Additionally, group III (and, to a lesser extent, II) demonstrated significant ischemia in adjacent non-embolized tissue, whereas groups I and IV had no ST elevations from baseline in the circumflex distribution at any time post-embolus ($P < 0.02$). All three animals in group V exhibited large ST segment elevations (greater than 5 mm) within 1 min post-embolus in both LAD and circumflex distributions.

Groups II and III also had a greater incidence of reperfusion dysrhythmias (defined as greater than six premature ventricular contractions per minute) than groups I and IV, and this was statistically significant at 5, 10, and 15 min post-embolus (table 4, $P < 0.02$). All three animals in group V developed malignant ventricular dysrhythmias within 1–2 min post-embolus. Two of these animals developed ventricular fibrillation within 1½ min, and one animal within 4 min, of CAE when nitrous oxide remained in the inspired gas mixture.

Discussion

Our model demonstrates the typical events associated with coronary air embolism: ECG changes typical for ischemia, ventricular dysrhythmias including ventricular fibrillation, transient increases in LVEDP, decreases in mean arterial pressure, cardiac output, LV dP/dt, and coronary blood flow.[11] Following dissolution or dispersion of intracoronary air, there is a variable period of post-ischemic reactive hyperemia. The duration of this hyperemia correlates with the severity of the ischemic event. Myocardial damage following air embolism results not only from blockage of vessels by air bubbles, but also from the reaction of blood elements to the air/bubble interface.[12] This may be responsible for endothelial injury, as well as decreases in coronary blood flow that persist even after resolution of the physical occlusion of a blood vessel by the air bubble.

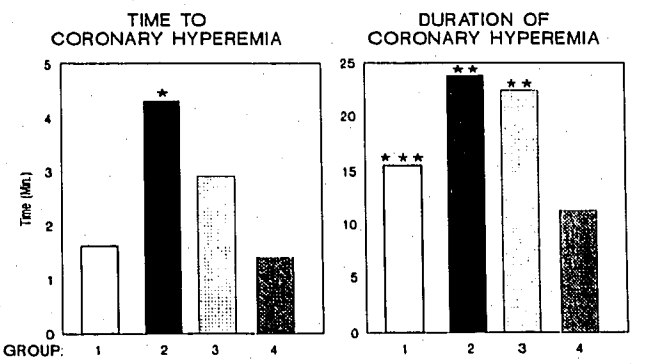

FIG. 3. Duration of coronary flow depression and duration of hyperemia after coronary embolism in groups I–IV. *Group 2 > 1 and 4, **Group 2 and 3 > 1 and 4, ***Group 1 > 4 ($P < 0.05$).

Coronary air embolism is probably more common than is recognized. A recent study showed that left heart and aortic air emboli were detectable by M-mode transesophageal echocardiography in 79% of patients having valvular operations and 11% of patients having coronary revascularization, even after routine air clearing maneuvers were applied.[13] Coronary air embolism was directly visualized by transesophageal echocardiography, and immediately followed by hemodynamic instability in this study. Retained air after cardiopulmonary bypass has been known to not only cause neurologic problems, but also to produce coronary air embolization, with subsequent myocardial ischemia and hemodynamic compromise during open heart surgery.[2-5,11] Anecdotal reports of sudden decompensation following the introduction of nitrous oxide after successful weaning from extracorporeal perfusion have appeared,[14] but there are no studies to date that conclusively demonstrate N_2O to be clearly responsible for worsening the sequelae of coronary air embolism.

TABLE 3. Regional Myocardial Lactate Extraction Ratios after CAE

Group	Baseline	5 min	15 min
I	.548 ± .173	.279 ± .072†	.488 ± .077
II	.417 ± .140	.037 ± .062*†	.240 ± .142*†
III	.489 ± .098	.138 ± .120†	.410 ± .072
IV	.440 ± .040	.180 ± .050†	.415 ± .073

Values are means ± standard deviation.
* Significantly different from Group I at these times ($P < 0.05$).
† Significantly different from baseline within group ($P < 0.05$).

TABLE 4. Electrocardiographic Changes and Coronary Embolus

Group	Area	# Animals with ST > 3 mm Time (Minutes) 1	3	5	10	15	# Animals with PVC > 6/min Time (Minutes) 1	3	5	10	15
I	LAD	1	0	0	0	0	1	1	0	0	0
	CIRC	0	0	0	0	0					
II	LAD	5*	6*	4*	2	1	2	3	4*	4*	4*
	CIRC	0	1	0	0	0					
III	LAD	6*	6*	6*	3	3	4	3	3*	3*	3*
	CIRC	5*	4*	3*	1	1					
IV	LAD	1	2	2	0	0	0	0	0	0	0
	CIRC	0	0	0	0	0					
V	LAD	3	2				3	3			
	CIRC	3	2								

LAD = embolized area; CIRC = nonembolized area. Group I–IV, N = 6; Group V, N = 3.

* Denotes $P < .02$ compared to group I at these times.

Our study documents that the myocardial insult after coronary air embolism is markedly enhanced in the presence of nitrous oxide. This appears to be a direct result of decreased coronary blood flow. Although difficult to quantitate, we observed that following coronary air embolization, the length of LAD segment containing gas and the area of ischemic cyanotic myocardium was far greater in the animals ventilated with N_2O than those not exposed to N_2O. Nitrous oxide is approximately 30 times more soluble in blood than is nitrogen, and therefore can diffuse from blood into the air embolism much more rapidly than nitrogen can be removed. The result is a rapid expansion of air embolus size, which will produce more widespread blockage of coronary flow. It has been demonstrated that bubbles as small as 100 microns may coalesce and be too large to traverse capillary beds.[15] Use of N_2O could make bubbles which would have passed through the microcirculation too large to do so. The use of a gaseous embolus containing the same fraction of N_2O as the inspired gas mixture (group IV) prevents the embolus from expanding, explaining the similarity of responses of groups I and IV. In fact, since the N_2O in the inspired gas mixture was discontinued at the time of gaseous embolus in group IV, one would predict that the embolus would actually resolve faster than an air embolus in non-N_2O ventilated animals (group I), since the N_2O in the embolus could move down its concentration gradient faster than nitrogen could be resorbed from an air embolus. This is consistent with the finding that group IV animals had the shortest time to reestablishment of baseline LAD coronary artery blood flow and the fastest recovery from hyperemia of all the groups. Similarly, by 15 min post-coronary embolization, group IV most closely approached baseline levels of regional myocardial lactate extraction of all the groups. Group IV had the lowest incidence of dysrhythmias of all the groups and, by 10 min post-embolus, there was no electrocardiographic ischemia in group IV (as well as group I). The above evidence and reasoning are supportive of the conclusion that the primary detrimental action of nitrous oxide in the presence of coronary air embolism is to enlarge the gas bubble.

There remain other reasons why nitrous oxide may produce such deleterious effects in the presence of coronary air embolism. Nitrous oxide has been shown to induce regional myocardial changes consistent with ischemia. These include decreased segmental systolic shortening and post-systolic prolongation of segmental contraction in areas of myocardium supplied by an acutely critically stenosed canine coronary artery.[10] Other recent studies have failed to demonstrate regional wall motion abnormalities in humans exposed to N_2O in the presence of flow-limiting coronary lesions.[16,17] Whether or not nitrous oxide causes regional wall motion abnormalities in situations of limited coronary flow, it has been shown to constrict epicardial coronary arteries,[18] producing increased resistance to blood flow, especially in the presence of coronary stenoses. Our data are consistent with this, since all groups of animals exposed to nitrous oxide had slightly lower (albeit not statistically significant) baseline LAD coronary artery blood flow than group I, even when coronary perfusion pressure was equalized to those animals not receiving nitrous oxide (fig. 2). The presence of coronary obstructions, embolus-mediated endothelial damage, and increased coronary vascular resistance may exacerbate any direct effects of flow blockage due to the embolus itself. Since coronary air embolism itself can produce both regional and global myocardial ischemia by acutely limiting coronary artery blood flow, the use of nitrous oxide in this setting must be questioned, even if it were not to increase embolus size.

Standard management of air embolism usually in-

cludes a recommendation to maintain or even elevate perfusion pressure of the embolized tissue[6] by pharmacologic or mechanical means in an effort to force air bubbles through the circulation, eliminate major flow occlusion, and provide adequate perfusion to compromised but still salvagable tissue. Our results indicate that maintaining coronary perfusion pressure at normal levels (group III) had no beneficial effect in minimizing coronary ischemia compared to animals in which the coronary perfusion pressure was not manipulated (group II). Although a reflexly lower heart rate in the alpha-adrenergic stimulated animals (group III, table 2) should improve perfusion of the myocardium by increasing diastolic perfusion time, this effect was not seen, despite normalization of coronary perfusion pressure. Our data does not allow us to test the hypothesis of whether elevation of coronary perfusion pressure to supra-normal levels would be beneficial in this setting.

Persistence of nitrous oxide in the inspired gas mixture was uniformally fatal in our model of coronary air embolism. Even when nitrous oxide was discontinued at the time of air embolization, the cardiovascular insult was not eliminated. During cardiac surgery, the presence of myocardial injury from cardioplegic arrest, as well as underlying coronary obstructive lesions, could markedly exacerbate the detrimental effects of nitrous oxide on coronary air embolism. Although nitrous oxide can be safely used prior to great vessel cannulation and institution of cardiopulmonary bypass, we believe that nitrous oxide should never be used after discontinuation of cardiopulmonary bypass, since the risk of coronary air embolization remains, and its effects are potentially devastating when nitrous oxide is present.

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