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Postsystolic Shortening of Canine Left Ventricle Supplied by a Stenotic Coronary Artery when Nitrous Oxide Is Added in the Presence of Narcotics

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The effects of fentanyl and sufentanil with and without N_2O on left ventricular myocardium supplied by a critically narrowed and a normal coronary artery were studied in 16 dogs. Regional ventricular function was measured by recording ventricular segment length with the use of ultrasonic length detectors in the left anterior descending (LAD) and the left circumflex (LC) coronary artery territories before and during critical stenosis of the LAD. Critical stenosis was documented by the absence of a hyperemic response following a 10-s total occlusion of the LAD. Hemodynamic variables (aortic flow and pressure, left ventricular pressure, heart rate, and coronary blood flow) were measured and the first derivative of left ventricular pressure (LVdP/dt) and coronary perfusion pressure derived. Eight dogs received fentanyl 100 $\mu g \cdot kg^{-1}$ followed by an infusion of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ while ventilated with O_2:N_2 (1:2), and eight dogs received sufentanil 30 $\mu g \cdot kg^{-1}$ with an infusion of 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Replacement of N_2 with N_2O produced evidence of mild systolic myocardial depression but no dysfunction in either group. After application of the critical constriction, the addition of N_2O rapidly produced evidence of dysfunction with significant postsystolic shortening only in the LAD territory. This was not accompanied by hypotension or a decrease in coronary flow and was not always reversible. Higher infusion rates of either narcotic (fentanyl 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$; sufentanil 0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 1.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in the absence of N_2O did not produce dysfunction but had no protective effect when N_2O was added. These data suggest that the addition of N_2O to a narcotic base anesthetic can produce clinically unapparent regional myocardial ischemia, which may be an important factor in the etiology of perioperative myocardial infarction. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, intravenous: fentanyl; sufentanil. Complications: myocardial ischemia. Heart: coronary artery disease; myocardial ischemia; ventricular function.)

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SEVERAL STUDIES have reported that volatile anesthetics can have deleterious effects upon regional myocardial function in areas of limited coronary blood flow.[1–3] The degree of dysfunction produced appears to be dose dependant, related to the hemodynamic effects, and secondary to an inappropriate decrease in coronary blood flow. The use of high doses of synthetic narcotic with and without nitrous oxide is a common practice in the anesthetic management of patients with coronary artery disease. However, there are no data available about the effects of such drugs on regional myocardial function. This study was undertaken to determine the effects of two synthetic narcotics, fentanyl and sufentanil, on regional ventricular function in the dog heart. Studies were performed both when coronary flow was unimpeded and when it was markedly limited by a critical constriction. A further aim of these studies was to determine whether nitrous oxide had any important effect on regional function when added to a narcotic anesthetic.

Methods

Sixteen mongrel dogs weighing between 14 and 25 kg were studied in two groups. Five dogs in each group were premedicated with morphine sulfate (0.1 $mg \cdot kg^{-1}$), and anesthesia was induced with thiopental 10 $mg \cdot kg^{-1}$, iv. Three dogs in each group were anesthetized without premedication. The trachea was intubated, and constant volume intermittant positive-pressure ventilation was instituted at a rate of 12 breaths/min with a mixture of oxygen/nitrogen (1:2). Carbon dioxide was added to the inhaled mixture to maintain end-tidal CO_2 at 5.3%. Anesthesia was maintained during surgical preparation with halothane (0.7–1.5%). Temperature, monitored at the mid esophagus, was maintained between 37° C and 38° C by a heating element incorporated in the operating table.

The left common carotid artery was exposed, and a stiff 14-gauge polyethylene catheter inserted and advanced to within 1 cm of the aortic valve for blood sampling and measurement of systemic arterial pressure

via a Statham® pressure transducer. An intravenous cannula was threaded via the femoral vein into the inferior vena cavae for infusion of 0.9% saline at a constant rate of 4 $ml \cdot kg^{-1} \cdot h^{-1}$ by an infusion pump.

A left thoracotomy was performed, the fifth and sixth ribs excised, and the heart exposed and suspended in a pericardial cradle. A cannula was inserted into the pulmonary artery via the outflow tract of the right ventricle for determining cardiac output using indocyanine green dye. A second rigid cannula was inserted into the left ventricle via a stab wound in the apical dimple and connected to a Statham® pressure transducer. The aortic root was dissected free of its fat pad, and an appropriate size electromagnetic flow transducer (SEM 230 SE Laboratories) was placed.

The left anterior descending coronary artery (LAD) then was dissected free distal to the second major diagonal branch. A 3-0 woven Dacron® suture was placed loosely about the artery and connected to a micrometer-controlled spring-suspended snare that could be tightened or loosened in increments of 0.001 in. An electromagnetic flow probe (SEM 230 SE Laboratories) of appropriate diameter was placed around the vessel proximal to the snare. A pneumatic occluder was positioned distal to the probe to obtain zero flow readings.

Two pairs of ultrasonic piezo-electric crystals were inserted into the subendocardial myocardium by the technique previously described.[1] One pair was implanted into the area supplied by the LAD coronary artery distal to the isolated segment, the other into the area supplied by the left circumflex coronary artery (LC) to serve as a control segment.

Regional myocardial function was assessed by obtaining continuous measurement of segment length between each pair of crystals based upon measurement of ultrasonic transit times.[4,5] The principles behind this technique have been well described.[4-6] Briefly, the instantaneous distance between a pair of crystals in proportional to the transit time of ultrasound because ultrasound has a constant velocity of 1.56 mm/μs in the myocardium. A continuous analogue signal of dynamic segment length is provided by a repetitive stimulation rate of 1 kHz. The transit time is calibrated in steps of 1 μs generated by a quartz-controlled oscillator.

The signals were recorded on Mingograf® 81 eight-channel recorder (Elema Schonander, Stockholm, Solna, Sweden) at a paper speed of 100 mm/s. As described previously[1] in a normal segment length recording, the distance between the two crystals is shortest at the end of systole (systolic shortening). This was defined as the time of closure of the aortic valve, determined by the time of return to zero of the aortic flow signal. End-diastolic length (EDL) was defined as the length at the instant of the initial upslope of LV dP/dt (the first derivative of left ventricular pressure). When there is myocardial depression, end-diastolic length is increased and the velocity and magnitude of systolic shortening are decreased. Ischemia produces a decrease in the velocity of shortening, and postsystolic shortening appears, which is abnormal. Progression of the ischemia can result in systolic lengthening rather than shortening with the shortening occurring during diastole. Diastolic shortening is ineffective in contributing to the pumping action of the heart. Aortic and left ventricular pressures also were recorded, as were aortic flow, aortic blood acceleration (by differentiation of the flow signal), and LV dP/dt. Stroke volume (obtained by integration of flow signal) was calibrated by simultaneous determination of the cardiac output with the use of indocyanine green.

Protocol

The purpose of this study was to determine the effect of both fentanyl and sufentanil on regional myocardial function in the presence and absence of nitrous oxide. This was measured first with normal coronary flow and then after the application of a critical constriction of the LAD. Progressively larger doses of narcotics were administered to determine if this altered the response.

After surgical preparation had been completed, the administration of halothane was discontinued and the dogs continued to be ventilated with the oxygen/nitrogen mixture (1:2). Approximately 15 min later, Group 1 received a loading dose of fentanyl (100 $\mu g \cdot kg^{-1}$ at a rate of 300 $\mu g \cdot min^{-1}$), followed immediately by a constant rate infusion of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Group 2 dogs received sufentanil 30 $\mu g \cdot kg^{-1}$ (rate 100 $\mu g \cdot min^{-1}$) as the initial dose plus an infusion of 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$. During a 45-min period of stabilization, instruments were recalibrated, blood gases analyzed, and the ventilator adjusted if necessary. The experimental measurements began a minimum of 5 h after premedication. Table 1 outlines the protocol followed.

Phase I: Normal Coronary Flow

In both groups of dogs, after the stabilization period, base line measurements were obtained and blood gases analyzed at the end of a 15-min period. Following this, in Group 1, nitrous oxide was substituted for nitrogen, 15 min allowed to elapse, and measurements repeated. Nitrogen then was substituted for N_2O for another 15 min and a third set of measurements obtained. Thus, in Group 1, with a fentanyl infusion of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, there were 16 measurements with the nitrogen mixture and eight with nitrous oxide.

Group 2 dogs were subjected to a similar sequence of nitrogen/nitrous oxide/nitrogen, except that in seven of the eight dogs it was repeated a second time, *i.e.*,

TABLE 1. Protocol

Group 1 (n = 8) Fentanyl 100 ug·kg^{-1} load Fentanyl Infusion 1 μg·kg^{-1}·min^{-1}	Group 2 (n = 8) Sufentanil 30 μg·kg^{-1} load Sufentanil Infusion 0.3 μg·kg^{-1}·min^{-1}
O_2–N_2	O_2–N_2
O_2–N_2O	O_2–N_2O
O_2–N_2	O_2–N_2
	O_2–N_2O
	O_2–N_2
Critical Constriction	
Fentanyl Infusion 1 μg·kg^{-1}·min^{-1}	Sufentanil Infusion 0.3 μg·kg^{-1}·min^{-1}
O_2–N_2	O_2–N_2
O_2–N_2O	O_2–N_2O
O_2–N_2	O_2–N_2
2 μg·kg^{-1}·min^{-1}	0.6 μg·kg^{-1}·min^{-1}
O_2–N_2	O_2–N_2
O_2–N_2O	O_2–N_2O
O_2–N_2	O_2–N_2
4 μg·kg^{-1}·min^{-1}	1.2 μg·kg^{-1}·min^{-1}
O_2–N_2	O_2–N_2
O_2–N_2O	O_2–N_2O
O_2–N_2	O_2–N_2

nitrous oxide reintroduced for 15 min followed by nitrogen again. This resulted in 15 periods with nitrous oxide in the eight dogs receiving sufentanil 0.3 μg·kg^{-1}·min^{-1} and 22 periods with the nitrogen mixture.

PHASE 2: CRITICAL CONSTRICTION

Following the control measurements in all dogs, critical constriction of the LAD was imposed by tightening the snare in increments of 0.05 in. until there was an obvious decrease in the pulsatile pattern of the coronary flow tracing. Thereafter, the snare was tightened in increments of 0.025 in until the first changes indicative of dysfunction occurred (postsystolic shortening). The snare was loosened slightly until these changes resolved and then slowly retightened in increments of 0.005 in. until they reappeared. The snare continued to be adjusted back and forth until there was no evidence of dysfunction, but following a 10-s total occlusion of the LAD there was no postocclusion hyperemic response (fig. 1).

Once a satisfactory and stable critical stenosis had been obtained and after a 20-min rest period, recordings and a blood sample for blood gases were obtained. Nitrous oxide then was substituted for the nitrogen for 15 min, measurements repeated, and nitrogen reintroduced for another 15 min and a third set of measurements obtained.

The infusion rate for each narcotic was then doubled (Fentanyl 2 μg·kg^{-1}·min^{-1}, sufentanil 0.6 μg·kg^{-1}·min^{-1}) and following the stabilization period, the sequence of nitrogen/nitrous oxide/nitrogen repeated. Infusion rates were doubled again (fentanyl 4 μg·kg^{-1}·min^{-1}; sufentanil 1.2 μg·kg^{-1}·min^{-1}) and the sequence repeated for the third time.

At the end of each experiment the LAD coronary artery was cannulated proximal to the flow probe and flow calibrations performed. Evans blue dye then was injected to determine the mass of left ventricular muscle supplied by the artery.

Seven hemoglobin dissociation curves were constructed in five dogs with N_2 and N_2O to determine P_{50}.[7]

COMPUTATION

The data were digitized manually and subsequently stored and analyzed on a Hewlett–Packard® calculator 9825A.

Mean arterial pressure (MAP) was calculated from the systolic and diastolic systemic arterial pressures (SAP, DAP).

Coronary perfusion pressure (CPP) was calculated in the conventional fashion as the difference between DAP and left ventricular end diastolic pressure (LVEDP).

Peak power was calculated as the product of peak aortic flow × SAP.

Cardiac output (CO) was determined from heart rate and stroke volume measured by the aortic flow meter.

Results were analyzed for statistical significance using a two-way analysis of variance and Student's paired *t* test with $P < 0.05$ considered significant.

Results

Since no differences were observed between the responses of premedicated and unpremedicated dogs, they were combined for data analysis. Blood gases were normal throughout in all dogs in both groups. N_2O had no effect on the P_{50} of five dogs studied.

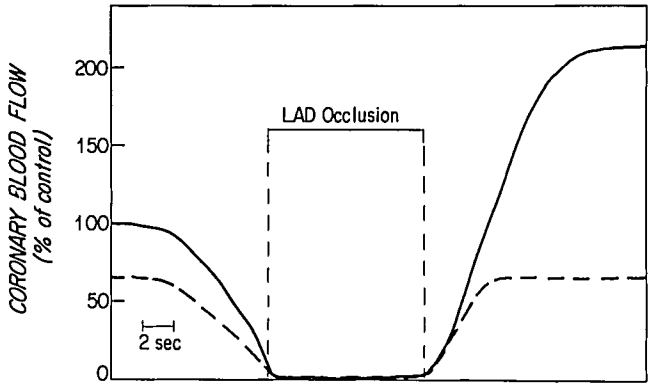

FIG. 1. The effect of critical constriction on coronary blood flow. After a 10-s occlusion, the hyperemic response is eliminated (dashed line) and flow returns only to the previous level.

TABLE 2. Effect of N_2O on Global Cardiac Function in Dogs with Normal Coronary Blood Flow

	Fentanyl N = 8		Sufentanil N = 15	
	N_2	N_2O	N_2	N_2O
LV dP/dt max (mmHg/s)	3,025 ± 151	2,631 ± 151*	2,950 ± 182	2,713 ± 188*
Ao. blood accel. (ml/s²)	8,427 ± 889	6,914 ± 528†	7,674 ± 428	6,851 ± 342*
Peak Power (mW)	4,679 ± 433	4,261 ± 359†	4,428 ± 357	4,357 ± 358
LVEDP (mmHg)	5.2 ± 0.4	5.6 ± 0.4	4.6 ± 0.3	5.5 ± 0.5†
CO (ml/min)	2,257 ± 186	2,370 ± 143	2,953 ± 271	2,801 ± 237

* $P < 0.01$. † $P < 0.05$.

PRECONSTRICTION

The addition of nitrous oxide to the Group 1 dogs (fentanyl 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) produced no significant changes in heart rate, arterial pressure, coronary blood flow, cardiac output, LVEDP, or coronary and systemic vascular resistance. LV dP/dt max, aortic blood acceleration, and peak power decreased significantly (table 2). The segment length data (table 3) demonstrate that the only significant change was in the end diastolic length (EDL) in the circumflex (control) segment.

The Group 2 dogs (sufentanil 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$) followed a similar pattern with the changes in LV dP/dt max, aortic blood acceleration, and LVEDP achieving significance (table 2). The length measurements demonstrated increases in EDL, which were significant in both segments studied. Systolic shortening was either decreased or unchanged, with no evidence of regional dysfunction (table 3) (fig. 2). An increase in EDL without an increase in systolic shortening is indicative of myocardial depression.

POSTCONSTRICTION

The application of the critical constriction resulted in a decrease in coronary flow in both groups of dogs (fentanyl 84 ± 4 to 58 ± 4 $ml \cdot min^{-1} \cdot 100\ g^{-1}$, sufentanil 111 ± 14 to 65 ± 4 $ml \cdot min^{-1} \cdot 100\ g^{-1}$).

In the Group 1 dogs (fentanyl) the addition of nitrous oxide in the presence of the critical constriction was followed immediately by the appearance of postsystolic shortening in the LAD distribution (fig. 3). This occurred at all infusion rates. One dog in this group developed evidence of permanent dysfunction after the initial nitrous oxide challenge and was dropped from the study. In the remaining seven dogs, discontinuation of the nitrous oxide resulted in a return within minutes to base line values at each infusion rate. The data thus were grouped for the three infusion rates (21 challenges) and are summarized in table 4 and figure 4.

The addition of the nitrous oxide produced a significant increase in EDL in both the LAD (11.99 ± 0.50 to 12.35 ± 0.54 mm $P < 0.001$) and LC (12.25 ± 0.05 to 12.59 ± 0.16 mm $P < 0.001$). A significant decrease in systolic shortening and marked increase in postsystolic shortening appeared only in the area supplied by the narrowed LAD and only in the presence of nitrous oxide (fig. 4).

The Group 2 dogs (sufentanil) presented a similar pattern of response. When digitizing the segment length recordings it became apparent that a small amount of permanent dysfunction following the initial N_2O challenge occurred (fig. 5). The data for all eight dogs (24 challenges) are presented in table 4 and figure 6. As in the previous group, the addition of nitrous oxide produced a significant increase in EDL in both the LAD (14.38 ± 0.65 to 14.78 ± 0.66 mm $P < 0.05$) and LC

TABLE 3. Effect of N_2O On Regional Cardiac Function in Dogs With Normal Coronary Blood Flow

	Fentanyl (N = 8)		Sufentanil (N = 15)	
	N_2	N_2O	N_2	N_2O
LAD				
EDL (mm)	12.01 ± 0.82	12.19 ± 0.78	13.97 ± 0.83	14.42 ± 0.88*
SS (mm)	2.70 ± 0.21	2.55 ± 0.22	3.49 ± 0.33	3.26 ± 0.36†
PSS (mm)	0.0	0.01 ± 0.01	0	0
LC				
EDL (mm)	12.18 ± 0.30	12.41 ± 0.28†	12.56 ± 0.69	13.04 ± 0.72
SS (mm)	2.35 ± 0.12	2.24 ± 0.09	2.26 ± 0.18	2.29 ± 0.19
PSS (mm)	0.11 ± 0.08	0.05 ± 0.04	0	0

LAD = left anterior descending coronary artery; LC = left circumflex coronary artery; EDL = end-diastolic length; SS = systolic shortening; PSS = postsystolic shortening.

* $P < 0.01$.
† $P < 0.05$.

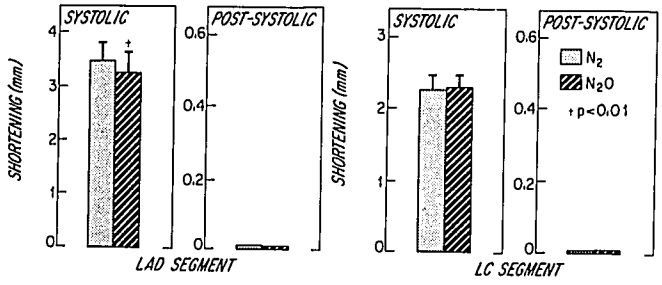

FIG. 2. Sufentanil—15 N_2O challenges in eight dogs. The effect of N_2O on regional function in the uncompromised heart with sufentanil 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion. Note that there was no increase in postsystolic shortening in either segment. Systolic shortening was decreased significantly in the LAD segment.

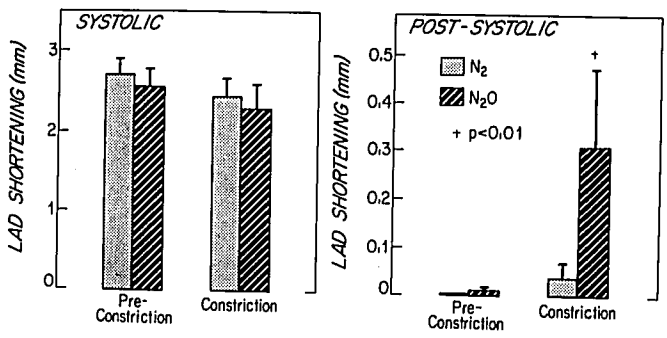

FIG. 3. Fentanyl—8 N_2O challenges in eight dogs. The effect of N_2O on regional function in the normal and compromised heart with fentanyl 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion. Postsystolic shortening was markedly increased in the compromised segment. The amount of decrease in systolic shortening was not affected by the constriction.

(13.13 ± 0.56 to 13.49 ± 0.58 mm $P < 0.001$). The marked increase in postsystolic shortening only appeared in the LAD distribution.

Increasingly larger infusion rates of either narcotic did not produce any evidence of regional dysfunction in the absence of nitrous oxide. Data from each period are presented in table 5 for the fentanyl group (seven dogs). It is apparent that even at the highest infusion rate (4 $\mu g \cdot kg^{-1} \cdot min^{-1}$) there was no significant change in length measurements. The hemodynamic effects were minimal and predictable, and none achieved statistical significance.

Table 6 contains similar data for the sufentanil group (eight dogs) and presents a similar pattern.

Discussion

The anesthetic management of patients with ischemic heart disease is an increasingly important clinical problem. The earlier studies that examined the interaction between anesthesia and the ischemic myocardium employed models with coronary artery occlusion, which mimics a recent myocardial infarction.[8,9] This has limited clinical relevance, however, since few of the patients with ischemic heart disease presenting for surgery have suffered a recent infarct. A far larger proportion of this population present with narrowed coronary arteries and limited or no reserve. Thus, it is important to study the effects of anesthetics in a model that is more analogous to the clinical situation.

Utilizing a model similar to the one in this study has the advantage of a preparation that has adequate coronary flow to meet basal requirements but is incapable of increasing flow to meet any increase in demand, thus, similar to an area causing angina pectoris. In such a model, the flow in the constricted artery is pressure dependent, since autoregulation has been exhausted. Previous studies have demonstrated that increasing concentrations of potent inhalation anesthetics could produce regional dysfunction in the area supplied by the constricted artery.[1,3] This was associated with a decrease in coronary flow secondary to the decrease in coronary perfusion pressure. It is recognized that regional dysfunction may occur in segments of the heart without an overall change in global performance.[2,10] Such changes can be detected only if sensitive indices of regional performance are utilized. Measurement of regional myocardial shortening in the subendocardium, used in our studies, is such a sensitive indicator.[1,11]

TABLE 4. Fentanyl—Critical Constriction—21 Challenges (Seven Dogs); Sufentanil—Critical Constriction—24 Challenges (Eight Dogs)

	Fentanyl		Sufentanil	
	N_2	N_2O	N_2	N_2O
Heart rate (beats/min)	97 ± 6	85 ± 3*	89 ± 4	87 ± 4
Mean BP (mmHg)	123 ± 4.2	119 ± 3.9	122 ± 4.2	118 ± 4.2†
LVEDP (mmHg)	5.1 ± 0.5	5.8 ± 0.4*	5.0 ± 0.3	6.0 ± 0.3*
Coronary perf. press. (mmHg)	101 ± 4	97 ± 3*	98 ± 2	93 ± 4†
Peak LV power (mW)	4,500 ± 230	4,040 ± 220‡	5,144 ± 340	4,431 ± 285‡
Cardiac output (ml/min)	2,090 ± 97	1,736 ± 82‡	2,328 ± 176	2,047 ± 150‡
Cor. blood flow ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)	58 ± 4	55 ± 5	65 ± 4	68 ± 5

* $P < 0.01$.
† $P < 0.05$.
‡ $P < 0.001$.

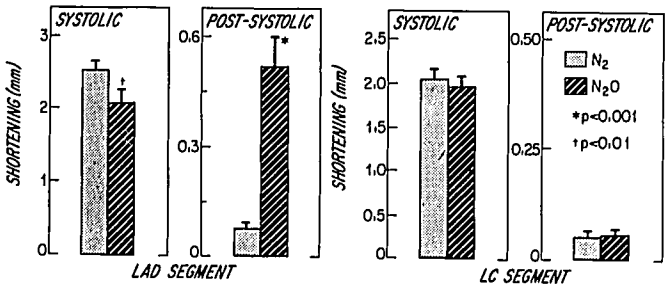

FIG. 4. Fentanyl—21 N_2O challenges in seven dogs. The effect of N_2O on regional function in the compromised heart. Data are grouped for the three infusion rates of fentanyl (see text). The marked increase in postsystolic shortening only occurred in LAD (compromised) segment.

One of the major advantages of the high-dose narcotic technique that is used widely in the management of patients with coronary artery disease is the lack of major hemodynamic effects and inferentially little change in the myocardial oxygen supply/demand ratio. Nitrous oxide often is used as a supplement and generally considered innocuous. The data accummulated in these studies allows us to make two important observations: the first, regarding the effect of the narcotic itself, and the second, concerning the effect of nitrous oxide added to the narcotic.

NARCOTIC EFFECT

Our data supply evidence that administration of high doses of narcotics are not associated with regional myocardial dysfunction even in the presence of significant restriction of coronary flow. A recent study has suggested that ischemia as evidenced by lactate production occurs commonly in areas of compromised flow with high-dose fentanyl anesthesia. The authors suggested that a redistribution of blood flow perhaps due to a reduction in coronary perfusion pressure might be responsible for their observations.[12] Under the conditions of the present study, coronary perfusion pressure and flow were maintained. If lactate production indicative of ischemia had occurred, presumably measurements of regional function would have reflected this. Thus, there was no evidence of ischemia or dysfunction at any infusion rate with either narcotic. Recent evidence contradicts the contention that myocardial ischemia is associated with high-dose narcotic anesthesia in humans with coronary artery diseases.[13] Our data support this.

It should be noted that under the conditions of the present study no stimulation of any sort occurred. Thus, we are observing only the drug effect. It is not unreasonable to suggest the possibility that in the face of the precarious balance existing with the critical stenosis imposed, external stimulation causing even a minimal decrease in flow or increase in demand could result in oxygen imbalance. Nonetheless, in the absence of such an effect neither fentanyl or sufentanil at any dose tested produced evidence of regional dysfunction.

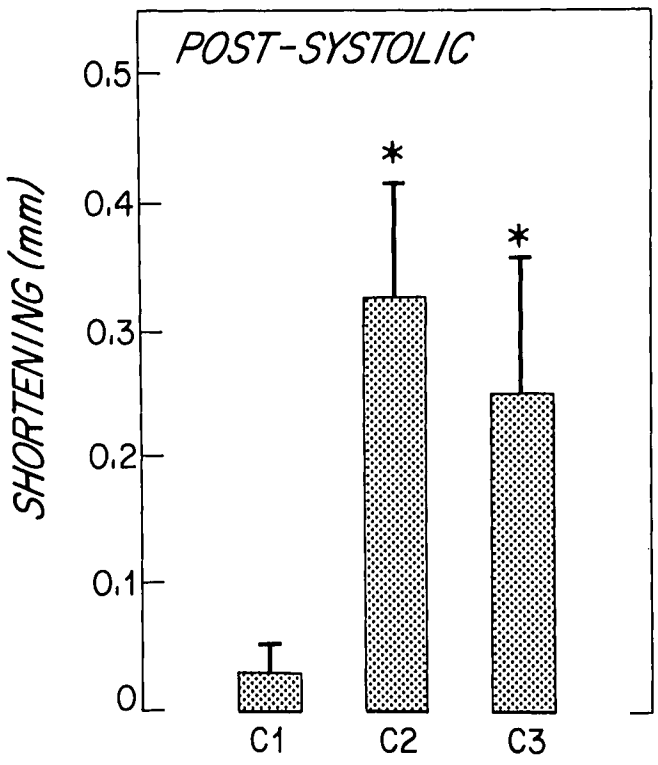

FIG. 5. A small but significant amount of postsystolic shortening was present in the control periods of sufentanil infusion after the initial N_2O challenge—C1—sufentanil 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$; C2—0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$; C3—1.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$s;1.

NITROUS OXIDE EFFECT

The addition of nitrous oxide prior to critical constriction resulted in changes compatible with mild systolic myocardial depression but no evidence of dysfunction in either group. This is suggested by the increase in

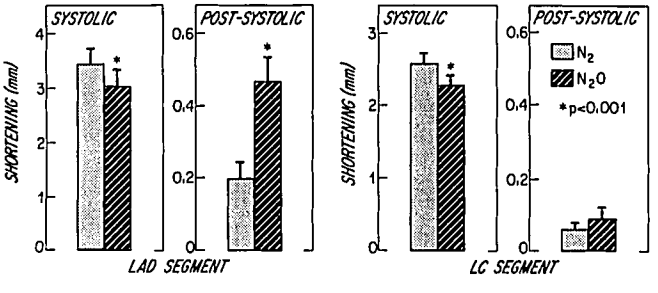

FIG. 6. Sufentanil—24 N_2O challenges in eight dogs. The effect of N_2O on regional function in the compromised heart. Data are grouped for the three infusion rates of sufentanil (see text). The significant increase in postsystolic shortening only occurred in the LAD (compromised) segment, although there was a small amount of dysfunction in both segments prior to the N_2O (see text for details).

TABLE 5. Effect of Increasing Infusion Rates of Fentanyl on Global and Regional Ventricular Function in Seven Dogs Postconstriction

	1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	2 $\mu g \cdot kg^{-1} \cdot min^{-1}$	3 $\mu g \cdot kg^{-1} \cdot min^{-1}$
Heart rate (beats/min)	102 ± 11	93 ± 8	96 ± 11
Mean BP (mmHg)	120 ± 7	127 ± 9	122 ± 11
Cardiac output (ml/kg)	2,237 ± 191	2,075 ± 150	1,974 ± 173
LVEDP (mmHg)	5.0 ± 0.8	5.3 ± 0.9	5.0 ± 0.8
LV dp/dt max $(mmHg/s)^{-1}$	3,129 ± 204	3,043 ± 258	2,914 ± 239
Ao Blood Accel. (ml/s^2)	7,617 ± 420	7,475 ± 412	6,524 ± 370
Coronary perf. press. (mmHg)	100 ± 6	103 ± 8	103 ± 6
Coronary blood flow $(ml \cdot min^{-1} \cdot 100\ g^{-1})$	59 ± 6	56 ± 7	54 ± 7
LAD			
EDL (mm)	11.9 ± 0.9	12.1 ± 0.9	12.1 ± 0.9
SS (mm)	2.54 ± 0.23	2.44 ± 0.33	2.47 ± 0.27
PSS (mm)	0.04 ± 0.03	0.11 ± 0.06	0.10 ± 0.04
LC			
EDL (mm)	12.2 ± 0.3	12.4 ± 0.3	12.3 ± 0.3
SS (mm)	2.0 ± 0.15	2.12 ± 0.12	2.0 ± 0.19
PSS (mm	0.07 ± 0.05	0.06 ± 0.04	0.17 ± 0.08

LAD = left anterior descending coronary artery; LC = left circumflex coronary artery; EDL = end-diastolic length; SS = systolic shortening; PSS = postsystolic shortening.

EDL that occurred and the decreases in LV dP/dt max, peak power, and aortic blood acceleration that accompanied it. An increase in EDL in the absence of depression would be expected to cause increased systolic shortening and contractility.

The most important new finding of this study was the consistant and significant deleterious effect that N_2O had on regional function in the area of compromised flow. This dysfunction was rapid in onset, of a considerable amount, often persistent, and not associated with a decrease in coronary blood flow. The nature of the dysfunction was a paradoxic shortening after the completion of systole (Fig. 7). This change may not be specific but is compatible with myocardial O_2 inbalance. Postsystolic shortening has been described as the earliest change accompanying myocardial ischemia.[1,14] Further studies will be needed to define precisely the mechanism for these changes. In one dog in the fentanyl group, dysfunction persisted for more than 1 h until termination of the experiment, despite the release of the snare and restoration of control coronary flow. This may support the recently postulated theory that ischemia is not a purely transient reversible process but may interfere with normal myocardial function, biochemical processes, and ultrastructure for prolonged periods or even permanently and may be associated with myocardial necrosis.[15,16]

It has been suggested that nitrous oxide reduces coronary flow and produces hypotension due to depression of the left ventricle, which may result in global ischemia in the presence of severe coronary disease.[17,18] While our data do present evidence of mild ventricular

TABLE 6. Effect of Increasing Infusion Rates of Sufentanil on Global and Regional Ventricular Function in Eight Dogs Postconstriction

	0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$	0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$	1.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$
Heart rate (beats/min)	91 ± 6	88 ± 7	86 ± 9
Mean BP (mmHg)	120 ± 6.5	124 ± 8.2	123 ± 7.9
CO (ml/kg)	2,362 ± 323	2,389 ± 339	2,233 ± 292
LVEDP (mmHg)	4.8 ± 0.3	4.9 ± 0.4	5.5 ± 0.6
LV dP/dt max (mmHg/s)	3,038 ± 236	3,000 ± 228	2,925 ± 223
Ao blood accel. (ml/s^2)	7,627 ± 551	7,795 ± 491	7,445 ± 602
Coronary perf. press (mmHg)	97 ± 7	100 ± 8	97 ± 8
Coronary blood flow $(ml \cdot min^{-1} \cdot 100\ g^{-1})$	70 ± 6	71 ± 9	62 ± 8
LAD			
EDL (mm)	14.13 ± 1.9	14.54 ± 1.14	14.31 ± 1.19
SS (mm)	3.49 ± 0.50	3.40 ± 0.52	3.44 ± 1.60
PSS (mm)	0.03 ± 0.02	0.33 ± 0.09*	0.25 ± 0.11*
LC			
EDL (mm)	12.96 ± 0.98	13.18 ± 0.99	13.26 ± 1.08
SS (mm)	2.53 ± 0.25	2.60 ± 0.26	2.58 ± 0.25
PSS (mm)	0	0	0

* $P < 0.05$ compared with column 1.
LAD = left anterior descending coronary artery; LC = left circumflex coronary artery; EDL = end-diastolic length; SS = systolic shortening; PSS = postsystolic shortening.

depression, the dysfunction we observed occurred in the absence of either hypotension or a reduction in coronary blood flow. Indeed, the addition of nitrous oxide consistently resulted in a decrease in heart rate that would have been expected to improve myocardial O_2 balance, nevertheless, regional dysfunction occurred. Thus, neither of these factors would appear to be a prerequisite for ischemia.

There was a small decrease in coronary perfusion pressure in both groups with the addition of nitrous oxide. This was a reflection of the slight decreases in diastolic pressure and slight increase in LVEDP. While these changes were small in magnitude, it is possible that in the face of the markedly compromised flow to the area involved, which is to a large extent pressure dependant, this would be sufficient to result in dysfunction. However, the actual coronary flow was unchanged (table 4).

It has generally been accepted that N_2O, and indeed most inhalational anesthetics, have a modest effect on the oxyhemoglobin dissociation curve, producing a small shift to the right.[19] Opiates do not have this effect.[20] A recent study has suggested, however, that N_2O is capable of producing a significant shift of the curve leftward.[21] This would necessitate unloading of oxygen at the tissue at a considerably lower Pa_{O_2}. Given the nature of this model, with a critical balance existing between supply and demand in the compromised area, such a shift might produce hypoxia and the appearance of regional dysfunction, even though measured Pa_{O_2} had not changed. While such a possibility is fascinating, it is not supported by the actual measurement of P_{50} in this series of dogs.

The maintance of coronary blood flow, as measured in this model, contains no information about the distribution of that flow beyond the stenosis. It is entirely possible that while total flow is not decreased, the relative distribution of the flow across the ventricular wall could be altered. Nitrous oxide is known to have a modest effect on the distribution of flow to various organ systems when combined with a potent inhalation agent.[22,23] Such effects have not as yet been well documented when N_2O is added to a narcotic anesthetic, although lack of deleterious effect on total coronary flow has been reported.[24,25] Conceivably, a shift of flow from the subendocardial to epicardial layers could occur, resulting in development of subendocardial ischemias as has been reported when dogs with a critical stenosis were exercised.[14] At present such an occurrence remains speculation.

It is important to note that in this model, regional and global ventricular function were normal and LVEDP relatively low prior to the addition of nitrous oxide. In the presence of an acute infarction or high LVEDP,

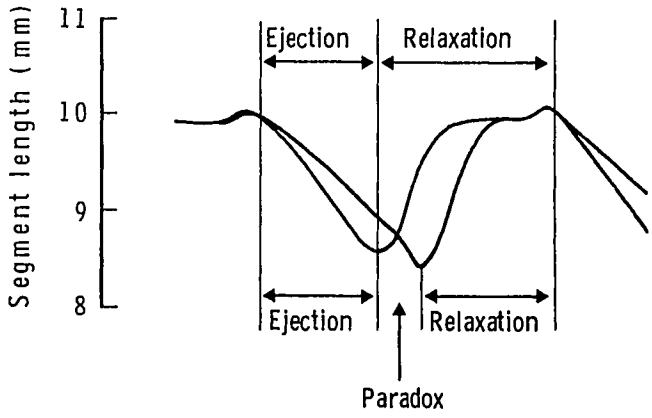

FIG. 7. Postsystolic shortening and relaxation. Note that in the abnormal (LAD) segment, shortening continues into the relaxation phase following ejection decreasing the relaxation period. In the normal segment, shortening ends with the end of ejection.

deleterious effects of nitrous oxide might be anticipated,[26,27] but the relatively small global hemodynamic changes that occurred in this study consistently were accompanied by evidence of definite regional dysfunction. It appears unlikely that such changes, in the clinical setting, would be a cause for alarm. This raises the disturbing possibility that such dysfunction undetected by the usual monitoring might progress or contribute to the later development of global dysfunction.[28] In this regard it is interesting that seven of 101 patients receiving N_2O–narcotic suffered a recurrent postoperative MI, compared with one of 216 receiving O_2–narcotics.[29] This empahsizes the need for a prospective study of this question.

In conclusion, neither fentanyl or sufentanil produce regional myocardial dysfunction, even in the face of markedly compromised coronary blood flow. The addition of nitrous oxide rapidly results in the appearance of postsystolic shortening limited to the regions supplied by a narrowed coronary artery. This dysfunction is not always reversible, and higher infusion rates of narcotic do not appear to have any protective effect.

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