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Hemodynamic Effects of Morphine and Morphine–Nitrous Oxide in Valvular Heart Disease and Coronary-artery Disease

Robert K. Stoelting, M.D., and Philip S. Gibbs, M.D.†*

Cardiovascular effects of morphine (1 mg/kg) with and without 60 per cent nitrous oxide were determined in spontaneously breathing patients before operation for aortic and/or mitral valve replacement or coronary artery reconstruction. In patients who had valvular heart disease infusion of morphine was associated with significantly increased cardiac index (CI) and stroke volume index (SVI) and decreased mean arterial pressure (MAP) and systemic vascular resistance (SVR). Ten minutes after completion of the infusion, all values had returned to near awake control levels except the elevated CVP and P_{aco_2}. Changes in the patients who had coronary-artery disease were in the same direction but less marked, and HR decreased significantly.

When nitrous oxide was substituted for nitrogen before operation or after cardiopulmonary bypass and during controlled respiration, MAP, CI, and SVI decreased in both groups to about the same degree. HR decreased significantly in patients with coronary-artery disease only. When nitrous oxide was discontinued, MAP and SVI returned to control values, but CI and HR remained depressed. Incision of the skin increased MAP and HR, but CI increased in the coronary-artery disease patients only.

The authors conclude that morphine produced transient peripheral vasodilation and cardiovascular stimulation in patients with heart disease. Changes were more prominent in patients with valvular heart disease. Nitrous oxide added to morphine produced cardiovascular depression in all patients before operation and after cardiopulmonary bypass. (Key words: Morphine; Nitrous oxide; Cardiovascular effects; Valvular heart disease; Coronary-artery disease.)

* Assistant Professor of Anesthesia and Pharmacology.
† Anesthesia Resident.
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INTRAVENOUS ADMINISTRATION of large doses of morphine (0.5–3.0 mg/kg) to critically ill cardiac surgical patients is a currently popular anesthetic technique. An important reason for this popularity is the apparent lack of detrimental hemodynamic changes following morphine. Lowenstein *et al.*[1] compared cardiovascular effects of 1 mg/kg morphine (10 mg/min) in patients with normal hearts with those in patients who had aortic-valve disease. Cardiac index, systemic vascular resistance, blood pressure, and pulse rate did not change in their "normal" group, while morphine uniformly increased cardiac index and decreased systemic vascular resistance in those needing aortic valve replacement.

As more experience was gained, limitations of morphine anesthesia for patients with fixed low cardiac outputs became apparent.[2] Although an excellent analgesic, morphine does not consistently produce loss of consciousness even in very ill patients, and total amnesia is not certain. Hypotension may occur during or following infusion of morphine, necessitating vasopressor administration. Painful stimulation usually produces movement in an unparalyzed patient, and the accompanying hypertension may be undesirable in a heart unable to increase its coronary blood flow.

Morphine anesthesia has also been used for patients undergoing operations for coronary artery reconstruction. Unlike the valvular heart disease group, these patients usually do not have fixed low cardiac outputs, and they tend to be in better overall general health. The deficiencies of morphine—particularly lack of unconsciousness or assured amnesia with morphine alone—are more apparent in these patients, and hypertension often follows painful stimulation. To diminish the possible un-

TABLE 1. Patient Data (Mean ± SE)

	Patients with Valvular Heart Disease	Patients with Coronary-artery Disease
Age (years)	51 ± 6.2	43 ± 4.3
Weight (kg)	61.5 ± 5.6	74.0 ± 5.9
Body surface area (m^2)	1.7 ± 0.08	2.0 ± 0.11

desirable effects of morphine, it is necessary to add other anesthetic drugs.

We speculated that nitrous oxide would be a logical supplement to morphine anesthesia. Previous work showed no cardiovascular depression when nitrous oxide was added to halothane anesthesia,[3, 4] and requirements for potent inhalation anesthetics are decreased by nitrous oxide.[5] Therefore, nitrous oxide added to morphine might provide needed amnesia without cardiovascular depression and might even permit a decrease in morphine dosage. Peripheral vasoconstriction following addition of nitrous oxide to halothane has been observed.[6] If vasoconstriction also accompanied the addition of nitrous oxide to morphine, this combination might protect against narcotic-induced peripheral vasodilation and subsequent hypotension.

This study reports hemodynamic effects of intravenously administered morphine (1 mg/kg) and morphine plus 60 per cent nitrous oxide when administered to patients with valvular or coronary-artery heart disease.

Methods

Seven patients with valvular heart disease (four with mitral-valve disease, two with aortic-valve disease and one with mitral- and aortic-valve disease) and seven patients with coronary-artery disease were studied before elective operation (table 1). Digitalis and diuretics had been discontinued for four days, and no patient was receiving beta-blocking drugs. Three patients with mitral-valve disease were in atrial fibrillation. All patients were premedicated with morphine (6–15 mg) and scopolamine (0.2–0.4 mg). Arterial (radial or ulnar artery) and central venous (external or internal jugular vein) monitors and electrocardiogram were placed on the patient's arrival in the operating room and values obtained were recorded continuously. The patient then breathed a mixture of oxygen and air by mask from the anesthetic machine. The air and oxygen flowmeters were adjusted to maintain inspired oxygen at 40 per cent, as indicated by a Beckman oxygen analyzer. After at least 5 minutes, dye-dilution cardiac outputs (indocyanine green dye and Beckman Cardiodensitometer) and arterial blood gases (Pa_{O_2}, Pa_{CO_2}, and *p*H) were determined. These measurements were considered the awake control values.

Morphine (1 mg/kg) was administered intravenously at a rate of 10 mg/min; repeat measurements were made midway through the infusion (3–5 minutes), at its completion (6–10 minutes), and 10 minutes later (17 minutes). Succinylcholine (1 mg/kg) was then administered to facilitate tracheal intubation, and controlled respiration was maintained with a volume ventilator. An infusion of succinylcholine (2.0 mg/ml) was started after intubation in every patient; the infusion rate was adjusted to prevent movement until the incision of the skin had been made. Thirty minutes from the beginning of the infusion of morphine (after about 10 minutes of controlled respiration), all measurements were repeated, and 60 per cent nitrous oxide was substituted for nitrogen. Measurements were repeated 3 and 10 minutes later. After 10 minutes nitrous oxide was discontinued, and the measurements were repeated with the patient breathing 40 per cent oxygen. The values obtained at 30 minutes were considered the control values for the nitrous oxide observations. Hemodynamic responses with morphine alone were measured 2 minutes after incision of the skin and compared with values obtained immediately before stimulation.

Following cardiopulmonary bypass, and with the chest closed (230 ± 15 minutes since the start of the morphine infusion in the valvular heart disease patients and 305 ± 20 minutes in those with coronary-artery disease), control determinations during breathing of 40 per cent oxygen were repeated, and 60 per cent nitrous oxide was again added for 10 minutes. Recovery measurements were made 3 and 10

TABLE 2. Blood-Gas Data (Mean ± SE)

	Valvular Heart Disease			Coronary-artery Disease		
	Pa_{O_2} (torr)	Pa_{CO_2} (torr)	pH	Pa_{O_2} (torr)	Pa_{CO_2} (torr)	pH
Before operation						
Awake control	130 ± 12.5	42.8 ± 1.7	7.39 ± 0.03	142 ± 5.7	38.4 ± 2.4	7.41 ± 0.02
Morphine infusion (3–5 min)	146 ± 14.6	42.5 ± 2.1	7.40 ± 0.03	139 ± 4.3	38.8 ± 2.4	7.38 ± 0.02
Morphine infusion complete (6–10 min)	120 ± 13.1	50.1 ± 2.1	7.38 ± 0.02	137 ± 5.8	42.8 ± 3.1	7.37 ± 0.02
Preintubation (17 min)	120 ± 15.2	58.1 ± 3.1	7.31 ± 0.03	117 ± 5.2	45.1 ± 2.7	7.46 ± 0.02
Pre-N_2O (30 min)	160 ± 8.6	39.0 ± 2.5	7.41 ± 0.02	148 ± 10.8	32.2 ± 2.3	7.46 ± 0.03
N_2O on (10 min)	173 ± 9.2	35.9 ± 2.1	7.43 ± 0.02	165 ± 10.1	30.0 ± 2.8	7.46 ± 0.02
N_2O off (10 min)	169 ± 8.5	33.2 ± 1.8	7.46 ± 0.02	156 ± 10.1	26.5 ± 2.0	7.52 ± 0.02
After cardiopulmonary bypass						
Control	116 ± 11.1	38.8 ± 2.6	7.40 ± 0.04	136 ± 22.6	31.4 ± 4.5	7.48 ± 0.03
N_2O on (10 min)	127 ± 15.1	40.6 ± 2.4	7.36 ± 0.02	116 ± 19.3	33.4 ± 4.3	7.45 ± 0.03
N_2O off (10 min)	126 ± 15.4	36.2 ± 2.1	7.40 ± 0.02	122 ± 19.6	33.4 ± 4.3	7.50 ± 0.03

minutes after substitution of nitrogen for nitrous oxide.

After the incision of the skin, other anesthetic drugs (droperidol, secobarbital, scopolamine, nitrous oxide, and halothane) were used in various combinations to provide adequate anesthesia until cardiopulmonary bypass was instituted. No additional anesthetic drugs were needed after completion of extracorporeal circulation. Incremental doses of dimethyltubocurarine were administered after the start of operation.

Measurement by gas chromatography of end-tidal nitrous oxide concentrations in three patients with valvular heart disease revealed concentrations of 50–55 per cent 3 and 10 minutes after addition of nitrous oxide. End-tidal nitrous oxide was less than 5 per cent 3–5 minutes after discontinuation of the inhalation anesthetic. A semiclosed circle absorption system with total flows of at least 10 l/min was used during the entire observation period.

Data from the valvular heart disease and coronary-artery disease patients were considered separately and analyzed for statistical significance by Student's t test.‡§

‡ $P < 0.05$.
§ $P < 0.01$.

Results

Acute cardiovascular effects of 1 mg/kg morphine administered at a rate of 10 mg/min are shown in figure 1. In patients with valvular heart disease, mean arterial pressure (MAP) and systemic vascular resistance (SVR) decreased (86 to 73 torr ‡ and 39 to 27 torr/l/min/m² ‡) at the conclusion of morphine administration, while cardiac index (CI) and stroke volume index (SVI) increased (2.1 to 2.4 l/min/m² § and 22 to 30 ml/beat/m² §). Heart rate (HR) did not change. All measurements except central venous pressure (CVP, 6.1 to 8.5 torr ‡) and Pa_{CO_2} (42 to 58 torr,§ table 2) returned to near awake control levels before tracheal intubation and controlled respiration.

In patients with coronary-artery disease, the only significant changes at the conclusion of infusion of morphine were decreased MAP (99 to 91 torr ‡) and HR (79 to 72 beats/min ‡). Ten minutes after morphine infusion no values were significantly different from awake control values except CVP (7.9 to 10.1 torr ‡) and Pa_{CO_2} (38 to 45 torr,‡ table 2).

Figure 2 shows the changes when 60 per cent nitrous oxide was substituted for nitrogen 30 minutes following the start of morphine. MAP and CI decreased (82 to 68 torr § and

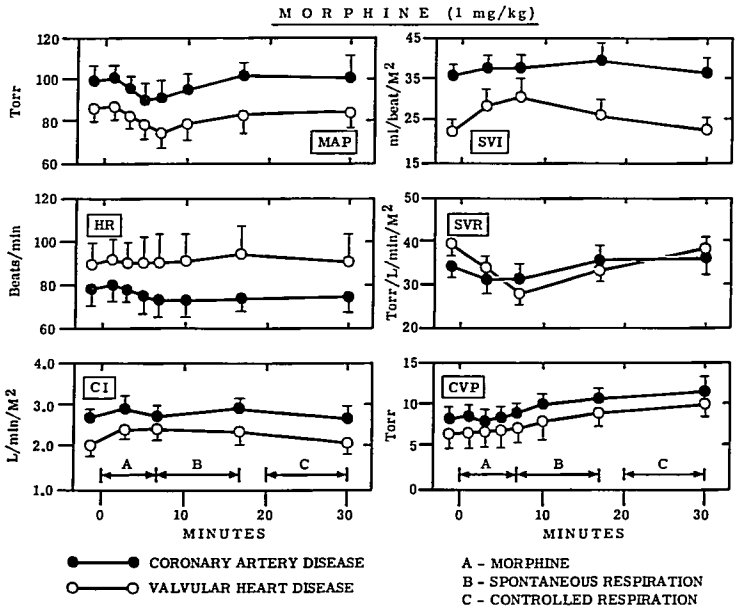

FIG. 1. Mean values ±SE during and after infusion of 1 mg/kg morphine at 10 mg/min. Spontaneous respiration was present during administration of morphine (*A*) and for about 10 minutes after completion of the infusion (*B*). All patients were intubated between 17 and 20 minutes, after which respiration was controlled (*C*). MAP, mean arterial pressure; HR, heart rate; CI, cardiac index; SVI, stroke volume index; SVR, systemic vascular resistance; CVP, central venous pressure. SE bars are drawn in one direction only to avoid overlap.

2.0 to 1.4 l/min m² §), while SVR increased after 10 minutes of administration of nitrous oxide to patients with valvular heart disease. HR had decreased 6 beats/min at the time of maximum blood pressure decrease. MAP and SVI returned to pre-nitrous oxide control values when nitrous oxide was discontinued, but CI § and HR remained depressed. Incision of the skin with morphine alone elevated MAP (78 to 93 torr §) and HR, but CI increased only slightly and SVI decreased compared with values immediately before stimulation.

Nitrous oxide administered for 10 minutes to patients with coronary-artery disease decreased MAP (99 to 86 torr ‡), HR (74 to 61 beats/min §), CI (2.6 to 1.7 l/min² §) and SVI (36 to 29 ml/beat/m² ‡), and SVR increased (36 to 44 torr/min/m² §). When nitrous oxide was discontinued MAP increased to above pre-nitrous oxide values, but HR,§ CI,§ and SVI remained depressed and SVR § continued to increase. Incision of the skin increased MAP (110 to 121 torr ‡), HR (65 to 80 beats/min ‡), and CI (2.1 to 2.7 l/min/m² §) to above values obtained immediately before stimulation.

Changes when nitrous oxide was substituted for nitrogen after cardiopulmonary bypass (fig.

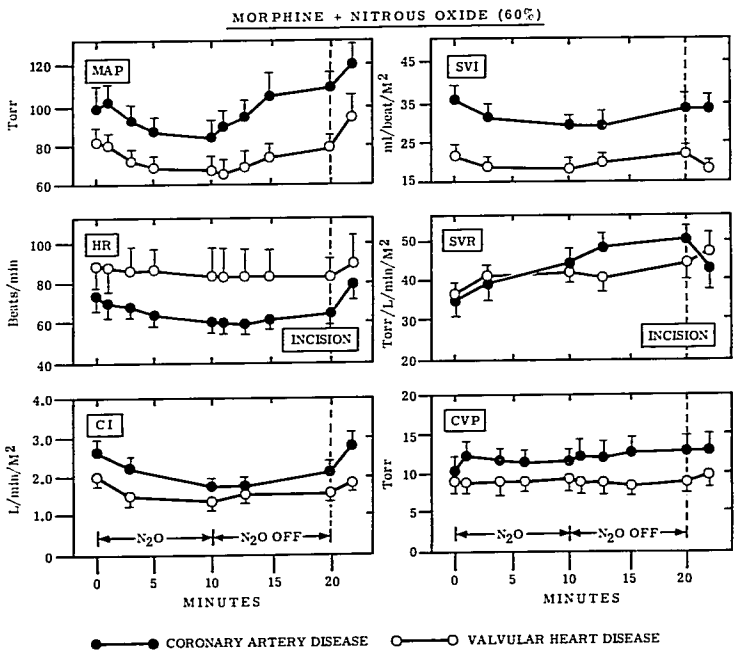

FIG. 2. Mean values ±SE when 60 per cent nitrous oxide was added for 10 minutes and then discontinued and measurements repeated for 10 additional minutes. After this, the incision of the skin was made, and measurements were repeated 2 minutes later. The 0 (control) values are those obtained 30 minutes after the start of the morphine infusion.

3) were similar to those before operation. Following valve replacement, the addition of nitrous oxide decreased MAP from 88 to 64 torr § and CI from 1.7 to 1.5 l/min/m² ‡ with return to control values when nitrous oxide was discontinued. SVR now decreased (48 to 35 torr/min/m² §) when nitrous oxide was added.

Ten minutes of administration of nitrous oxide after coronary artery reconstruction decreased MAP (102 to 76 torr §), HR (99 to 90 beats/min ‡) and CI (1.8 to 1.5 l/min/m² ‡), with return to control values when nitrous oxide was discontinued.

‡ $P < 0.05$.
§ $P < 0.01$.

Severe hypotension occurred in six patients (two with mitral-valve disease, two with aortic-valve disease and two with coronary-artery disease) during or following infusion of morphine, necessitating vasopressor administration. Blood pressures returned promptly to control levels, but data for these patients are not included in this report. Retrospective reviews of their charts did not reveal any patient differences that might help predict unusual cardiovascular sensitivity to morphine. Awake values and mean morphine dose administered to these patients were similar to those for patients who did not develop severe hypotension.

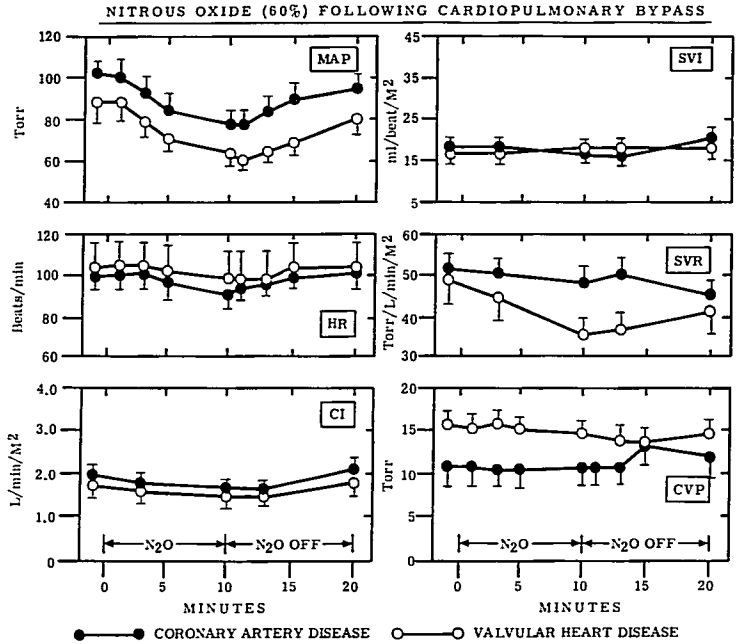

FIG. 3. Mean values ±SE when 60 per cent nitrous oxide was added and withdrawn following cardiopulmonary bypass.

Discussion

The presence of increased CI and decreased SVR during infusion of morphine in patients with valvular heart disease agrees with findings of Lowenstein *et al.*[1] 5–60 minutes after giving a similar dose of morphine to patients with aortic-valve disease. Unlike their findings, our patients' values returned to control levels 10 minutes after completion of the morphine infusion. During this time, Pa_{CO_2} had increased from 42 to 58 torr, while in Lowenstein's report Pa_{CO_2} did not increase significantly.

As in patients with valvular heart disease, infusion of morphine in patients with coronary-artery disease produced a transient decrease in MAP, which then returned to control values. CI increased only slightly, unlike the greater stimulation seen in those with chronically low cardiac outputs, and SVR did not decrease significantly. Hypoventilation was less in the patients with coronary-artery disease, as evidenced by a maximum Pa_{CO_2} elevation to 45 torr. Lowenstein *et al.*[1] reported no significant change in CI or SVR and less respiratory depression following administration of morphine to their normal patients. They speculated that increased adrenergic activity and respiratory physiologic deadspace present in patients with congestive heart failure may have contributed to the more prominent changes following infusion of morphine in their patients with vascular heart disease.

Hypercarbia in awake patients has been reported to increase cardiac output and HR, while SVR and mean right atrial pressure decreased.[7] It is tempting to suggest that elevated Pa_{CO_2} was responsible for the changes observed in our patients—particularly the greater cardiovascular stimulation seen in the patients with valvular heart disease. However, the greatest hemodynamic changes occurred during administration of morphine, when Pa_{CO_2} was not greatly altered, and measurements had returned almost to control levels 10 minutes after morphine infusion, when Pa_{CO_2} was maximally elevated (table 2). CVP's were significantly increased at this time in both groups. Patients with coronary-artery disease had higher awake venous pressures than those with valvular heart disease (6.1 *vs.* 7.9 torr), but the absolute increases were nearly the same in the two groups. Increases in mean right atrial pressure have been observed during administration of most inhalation anesthetics and attributed to direct myocardial depression.[8] Morphine-related myocardial depression might explain the elevated CVP after drug administration in our patients, but other cardiovascular measurements were not depressed at this time. Lowenstein *et al.*[1] also reported elevated CVP, and speculated that an altered ventilation pattern following administration of morphine could be responsible.

Cardiovascular depression following addition of nitrous oxide was evidenced by decreased MAP's and SVI's and dramatic decreases in CI in both patient groups. Although starting control levels were different, per cent depressions from control were similar for the two groups. Nitrous oxide was associated with decreased HR's in both groups, but this was significant in the coronary-artery disease patients only. The decreased HR at the time of MAP depression suggested vagal stimulation by nitrous oxide or decreased baroreceptor response. HR also decreased in the coronary-artery disease patients during morphine infusion with blood pressure decreased, suggesting a similar action of this drug.

We speculate that nitrous oxide produced cardiovascular depression and that the decreased blood pressure reflected the decrease in CI. MAP increased but CI remained depressed after nitrous oxide was discontinued, suggesting continued myocardial depression at a time when blood pressure indicated recovery. Similar effects of nitrous oxide after cardiopulmonary bypass suggested that cardiovascular depression from this combination persisted for some time after the initial administration of morphine. However, the use of other anesthetic drugs after morphine made evaluation of these data difficult.

Cardiovascular depression when nitrous oxide was added to morphine was somewhat surprising in view of the reported release of catecholamines by nitrous oxide and its peripheral sympathomimetic effect when added to halothane in healthy volunteers.[6] Nitrous oxide added to about 0.6 per cent end-tidal halothane produced no detectable cardiovascular depression in another group of patients with valvular heart disease.[4] However, Martin *et al.*[9] reported decreased cardiac output when 70 per cent nitrous oxide was added an hour after administration of 2 mg/kg morphine to healthy volunteers. Morphine premedication has also been reported to prevent the increased cardiac output seen when cyclopropane is administered.[10]

Surgical stimulation could prevent cardiovascular depression when nitrous oxide is used to supplement morphine anesthesia. Certainly, nitrous oxide has been used with morphine and hypotension not appreciated—in fact, nitrous oxide is often used when painful stimulation produces hypertension and tachycardia in a patient lightly anesthetized with morphine. It is possible that our patients were more adequately anesthetized when nitrous oxide was added. This might explain a small decrease in HR, but depression of MAP and CI from fairly normal control values suggested that nitrous oxide was producing cardiovascular depression rather than a more adequate anesthetic state. Hypotension and decreased CI after cardiopulmonary bypass when nitrous oxide was added suggested that surgical stimulation was not protective at that time.

Hypertension was a frequent problem, particularly during intubation and at the time of incision of the skin. CI's increased to near awake control levels in the coronary-artery disease patients two minutes after incision of the

skin, in contrast to those with valvular heart disease, in whom flow increased only slightly. MAP's and HR's increased in both groups. Increased myocardial work and oxygen requirements following painful stimulation may be detrimental in a heart which cannot increase its oxygen delivery because of valvular or coronary-artery disease.

We conclude that morphine produced transient peripheral vasodilation and cardiovascular stimulation during its infusion. These changes were more prominent in patients with valvular heart disease, as was the degree of hypoventilation. Nitrous oxide added to morphine produced similar degrees of cardiovascular depression in the two groups. That observed changes were, in fact, the result of morphine and/or nitrous oxide was suggested by the return of most hemodynamic measurements to control levels with time or following substitution of nitrogen for nitrous oxide.

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Obstetrics

PARACERVICAL BLOCK AND FETAL BRADYCARDIA Fetal bradycardia followed paracervical block anesthesia with mepivacaine (200 mg) in 24 of 92 patients who received 100 paracervical blocks. Gestational age, parity, fetal weight, and maternal complications did not influence the incidence of fetal bradycardia following paracervical block. There was a significant decrease in fetal *p*H and an increase in base deficit only when bradycardia lasted more than 10 minutes. Recovery from the transient metabolic acidosis was complete in all. Transient increases in uterine activity, as measured by the area under the uterine pressure curve, were found in the majority of patients with post-paracervical-block fetal bradycardia. Most patients who had no fetal bradycardia had decreases in uterine activity. (*Roger, K. F., and others: Fetal Cardiac Response to Paracervical Block Anesthesia, Am. J. Obstet. Gynecol. 113: 583–591, 1972.*)