Anesthesiology
61:385–393, 1984

Failure of Intravenous Nitroglycerin to Prevent Intraoperative Myocardial Ischemia during Fentanyl–Pancuronium Anesthesia

Ian R. Thomson, M.D., W. Alan C. Mutch, M.D.,† John D. Culligan, M.D.**

Twenty patients undergoing coronary artery bypass grafting under fentanyl–pancuronium anesthesia were studied. Continuous electrocardiographic (ECG) recording by a Holter Monitor was utilized to determine the incidence of ECG changes of myocardial ischemia during the precardiopulmonary bypass period and to determine the efficacy of an intravenous nitroglycerin (iv NTG) infusion for preventing ischemic ECG changes. Patients in Group 1 (n = 9) received a 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ iv NTG infusion 20 min prior to induction of anesthesia and throughout the study. Patients in Group 2 (n = 11) received placebo. A randomized double-blind protocol was employed. Anesthesia was induced with fentanyl 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$. After fentanyl 25 μg/kg and pancuronium 0.1 μg/kg, the trachea was intubated. After fentanyl 50 μg/kg surgery commenced. Prior to induction of anesthesia, iv NTG caused significant decreases in mean arterial pressure and pulmonary capillary wedge pressure, whereas placebo had no effect. However, subsequent to induction of anesthesia, hemodynamics in the two groups were identical. Fifty per cent of patients developed ECG changes of myocardial ischemia during the period from induction of anesthesia to commencement of cardiopulmonary bypass. The incidence of ischemic ECG changes was virtually identical in Group 1 (5/9) and Group 2 (5/11). Ischemic ECG changes were associated with increases in heart rate, mean arterial pressure, and rate pressure product, and decreases in the endocardial viability ratio (DPTI/SPTI). Increases in pulmonary capillary wedge pressure were not associated with myocardial ischemia. Fentanyl–pancuronium anesthesia, as administered in this study, was associated with a high incidence of myocardial ischemia. Ischemia was related to deteriorating myocardial oxygen balance resulting from the cardiovascular effects of anesthetic induction, endotracheal intubation, and surgery. Intravenous NTG was not superior to placebo for the prevention of ECG changes of myocardial ischemia during fentanyl–pancuronium anesthesia for coronary artery surgery. (Key words: Anesthetics, intravenous: fentanyl. Heart: electrocardiography. Neuromuscular Relaxants: pancuronium. Surgery: cardiac.)

PREVENTING intraoperative myocardial ischemia is a major goal of anesthetic management in patients with coronary artery disease (CAD) undergoing coronary artery bypass grafting (CABG). Intraoperative myocardial ischemia is thought to occur most commonly as a result of disproportionate elevation of myocardial oxygen demand, in excess of supply, in association with stress-related increases in heart rate, afterload, and myocardial contractility.[1] Fentanyl–pancuronium anesthesia has been advocated for patients undergoing CABG because it provides hemodynamic stability and prevents neuroendocrine stress responses.[2–4] Other investigators report adverse hemodynamic changes[5,6] and biochemical evidence of intraoperative myocardial ischemia[7] during fentanyl–pancuronium anesthesia for CABG.

Organic nitrates such as nitroglycerin (NTG) are of established value in the treatment of CAD.[8] The mechanism of action of NTG is controversial, and relief of ischemia has been attributed both to systemic and coronary vasodilation.[9] Intravenous NTG has been reported to relieve intraoperative myocardial ischemia during CABG[10] and to prevent perioperative myocardial ischemia in patients with angina pectoris undergoing noncardiac surgery.[11] We postulated that a prophylactic iv infusion of NTG would reduce the incidence of intraoperative myocardial ischemia during fentanyl–pancuronium anesthesia in patients undergoing CABG.

Abbreviations

BSA = body surface area
CABG = coronary artery bypass grafting
CI = cardiac index
CO = cardiac output
CVP = central venous pressure
DPTI/SPTI = diastolic pressure time index/systolic pressure time index
ECG = electrocardiogram
HR = heart rate
LVEDP = left ventricular end-diastolic pressure
MAP = mean arterial pressure
NTG = nitroglycerin
PAP = pulmonary artery pressure
PCWP = pulmonary capillary wedge pressure
RPP = rate pressure product
SAP = systolic arterial pressure
SVRI = systemic vascular resistance index

Derived Variables

$BSA = \text{height (cm)}^{0.725} \times \text{weight (kg)}^{0.425} \times 71.84 \times 10^{-4}$
$CI = CO/BSA$
$RPP = HR \times SAP$
$SI = CI/HR$
$SVRI = [(MAP - CVP)/CI] \times 79.9$

* Associate Professor, University of Manitoba.
† Lecturer, University of Manitoba.
Received from the Department of Anesthesia, St. Boniface General Hospital, University of Manitoba, 409 Tache Avenue, Winnipeg, Manitoba, R2H 2A6, Canada. Accepted for publication March 6, 1984. Supported by a grant from the Manitoba Health Research Council. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, October 1982, Las Vegas, Nevada.
Address reprint requests to Dr. Thomson.

TABLE 1. Hemodynamic Measurement Times

1. Control, pre NTG/placebo infusion
2. 20 min NTG/placebo infusion
3. Fentanyl 25 μg/kg and pancuronium 0.1 mg/kg
4. 1 min postintubation
5. 5 min postintubation
6. Fentanyl 50 μg/kg
7. 1 min after skin incision
8. 1 min after sternotomy
9. Pericardium open

Our investigation of fentanyl–pancuronium anesthesia for CABG had three main objectives: 1) to quantitate the incidence of electrocardiographic (ECG) changes of myocardial ischemia during the period prior to cardiopulmonary bypass; 2) to determine the hemodynamic variables associated with ischemic ECG changes; 3) to determine the efficacy of a prophylactic iv NTG infusion for prevention of intraoperative ECG changes of myocardial ischemia.

Methods

Twenty patients scheduled for elective CABG were studied and randomly assigned to one of two groups. Group 1 (n = 9) received iv NTG, and Group 2 (n = 11) received iv placebo. All patients had stable angina pectoris and were receiving beta-adrenergic blocking agents and organic nitrates. No patient was receiving a calcium-entry blocking agent. Only patients with normal complexes in leads II and V5 of their resting ECG were studied. This study received institutional approval, and informed consent was obtained from each patient. Organic nitrates and beta-blockers were withheld from midnight of the evening prior to surgery. Following premedication 1 h preoperatively with diazepam 0.15 mg/kg po, morphine 0.1 mg/kg im, and atropine 0.007 mg/kg im, nasal oxygen (3 l/min) was administered. Upon arrival in the operating room, ECG leads II and CS_5 were recorded continuously by a battery-operated Del-Mar Avionics Holter Monitor®. Under local anesthesia, intravenous, radial artery, and thermodilution pulmonary artery catheters were inserted. A separate peripheral iv delivery system, shown *in vitro* to be nonadsorptive for NTG, was used to administer either NTG 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or an equivalent amount of placebo. This infusion was continued throughout the study period. A double-blind protocol was followed.

After 20 min of NTG or placebo infusion, 100% oxygen was administered by mask and anesthesia was induced with fentanyl 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ iv. Pancuronium iv was administered in increments to relieve muscle rigidity and facilitate endotracheal intubation. Ventilation first was assisted then controlled. Following fentanyl 25 μg/kg and pancuronium 0.1 mg/kg, the patients were intubated and ventilated with oxygen. After a total of 50 μg/kg of fentanyl, surgery commenced. Fluids were administered at the discretion of the anesthetist. In order to avoid significant hypotension on induction, patients who had low cardiac filling pressures following NTG or placebo infusion received enough iv crystalloid solution to restore hemodynamics toward preinfusion values prior to and during the early stages of induction. Additional fentanyl (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was administered to patients who developed hypertension or tachycardia in response to surgery. The study was terminated when cardiopulmonary bypass (CPB) was begun. Complete hemodynamic measurements were made at the times indicated in table 1. Arterial pressure, pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), and central venous pressure (CVP) were recorded by a four-channel Hewlett-Packard® polygraph (Model 78304A) and transducers (Model 1280). Thermodilution cardiac output (CO) determinations were made in triplicate, using an Edwards Laboratory Cardiac Output Computer (Model 9520) and injections of 10 ml of iced 5% dextrose in water. Derived hemodynamic variables included heart rate (HR), cardiac index (CI), systemic vascular resistance index (SVRI), rate pressure product (RPP), and diastolic pressure time index/systolic pressure time index (DPTI/SPTI). The DPTI/SPTI ratio, an index of myocardial oxygen balance, was determined by planimetry from the arterial pressure trace and mean PCWP as described by Buckberg *et al.*[12] The average of three representative pulses was employed. Solutions of NTG were prepared from 0.6 mg tablets (Eli Lilly Company) dissolved in 0.9% sodium chloride. Arterial blood gases were determined prior to NTG or placebo infusion and immediately prior to skin incision. The Holter Monitor® ECG recordings were evaluated using an Avionics Electrocardioscanner. One of us screened the recordings and obtained representative 15 s writeouts of leads II and CS_5 from the time periods corresponding to the hemodynamic measurements listed in table 1. These representative ECG strips were then coded and jumbled. Another investigator then evaluated each ECG strip separately for evidence of myocardial ischemia, without knowledge of which patient, treatment group, or time interval was being evaluated. The ST segment was evaluated with respect to the PQ junction at a point 60 ms following the S wave nadir. Myocardial ischemia was diagnosed when persistent ST segment depression ≥ 1 mm at a calibration of 10 mm/mV was observed in either lead II or CS_5. Each ECG recording then was screened carefully for additional ischemic episodes between hemodynamic measurements. Analysis of variance was used to search for significant hemodynamic changes within and differences between treatment groups. A probability of $P < 0.05$ was regarded as

statistically significant. When analysis of variance revealed significant effects Student's t test was used to make multiple comparisons. Bonferroni's correction ($P < [0.05/k]$ for k comparisons) was used to compensate for the use of multiple t tests. Analysis of covariance was used to investigate the relationship between hemodynamic variables and ECG data.[13] The Wilcoxon–Mann–Whitney rank sums test was used to make intergroup comparisons of ordinal data.

Results

Table 2 compares Group 1 (NTG) and Group 2 (placebo) with respect to age, sex, ejection fraction, left ventricular end-diastolic pressure (LVEDP) at heart catheterization, daily dose of beta-adrenergic blocking agent, fentanyl dose, and volume of iv crystalloid administered prior to cardiopulmonary bypass. No significant differences were noted between groups. To compare the severity of coronary pathology in the two groups (table 3), we classified patients according to the number of coronary bypass grafts they received. Despite randomization, patients in Group 1 received a significantly larger number of bypass grafts than those in Group 2 ($P < 0.01$, Wilcoxon–Mann–Whitney ranks sums test).

The hemodynamic data from Group 1 (NTG) and 2 (placebo) are summarized in table 4. In Group 1, a 20-min iv NTG infusion produced significant decreases in MAP and PCWP. Significant decreases from control in MAP also were noted at several times subsequent to induction of anesthesia. The SVRI was significantly decreased at 5 min postintubation in Group 1. In Group 2, a 20 min iv placebo infusion had no significant hemodynamic effects. Heart rate was increased significantly following induction of anesthesia in Group 2 and remained increased until the time of skin incision. A decrease in SVRI was noted at 5 min postintubation in Group 2. Although the NTG and placebo infusions were continued throughout the study period, hemodynamics in Groups 1 and 2 were very similar subsequent to induction of anesthesia. Analysis of variance revealed no significant "between-groups" difference in hemodynamics when all time periods were considered. All patients had normal blood gases at control and following intubation.

The incidence and temporal distribution of ischemic ECG changes is summarized in figure 1 and table 5. Three patients showed ECG evidence of ischemia during the control period, prior to NTG or placebo infusion. These ECG changes subsequently resolved and the ST segment was isoelectric in all patients immediately prior to induction of anesthesia. Fifty per cent of patients (10/20) subsequently manifested ST segment depression

TABLE 2. Preoperative Characteristics and Intraoperative Variables for Groups 1 and 2 (Mean ± SEM)

	Group 1 (n = 9)	Group 2 (n = 11)
Age (yr)	54.4 ± 3.0	56.2 ± 2.3
Weight (kg)	82.0 ± 3.4	83.7 ± 2.1
LVEDP at heart cath (mmHg)	15.4 ± 1.3	15.6 ± 1.3
Ejection fraction	0.64 ± 0.05	0.62 ± 0.04
Daily dose of propranolol (mg/day)*	148 ± 24	188 ± 36
Total fentanyl dose (μg/kg)	58 ± 2	54 ± 4
Total crystalloid prebypass (l)	1.3 ± 0.6	0.8 ± 0.4

Group 1 (iv nitroglycerin); Group 2 (placebo).
* Four patients were taking beta-blockers other than propranolol. The equivalent daily dose of propranolol was estimated for those patients. (Some information taken from Frishman W: Clinical pharmacology of the new beta-adrenergic blocking drugs. Part I. Pharmacodynamic and pharmacokinetic properties. Am Heart J 97:663–670, 1979).

indicative of ischemia at some time subsequent to induction of anesthesia. Five patients developed ischemia prior to endotracheal intubation with the peak incidence of ischemia (8/20) following intubation. The incidence of ischemia was not influenced by nitroglycerin infusion. Five of nine patients in Group 1 and 5/11 in Group 2 developed ischemic ECG changes during the period prior to cardiopulmonary bypass.

Because iv NTG influenced neither hemodynamics postinduction nor the incidence of intraoperative ECG changes, the data from all 20 patients were combined in order to clarify the analysis of the overall hemodynamic effects of fentanyl–pancuronium anesthesia and allow a retrospective search for variables that were associated with ECG changes of ischemia.

The combined hemodynamic data from all 20 patients are summarized in table 6. Heart rate was increased significantly following induction of anesthesia and remained increased throughout the study. Cardiac index was increased significantly following endotracheal intubation. Significant decreases were noted in MAP, PCWP, and SVRI. No significant change in RPP or DPTI/SPTI occurred during the study.

TABLE 3. Number of Coronary Bypass Grafts Received in Group 1 (NTG) and Group 2 (Placebo)

	Number of Grafts					
	1	2	3	4	5	Total
Group I	0	2	2	2	3	9
Group II	3	2	5	1	0	11

The groups differ significantly $P < 0.01$ with respect to the number of bypass grafts received. (Wilcoxon–Mann–Whitney rank sums test).

TABLE 4. Hemodynamic Variables for Group 1 (n = 9) and Group 2 (n = 11) (Mean ± SEM)

Time Period	Control	20 Min NTG/ Placebo	25 μg	1 Min Postintubation	5 Min Postintubation	50 μg	1 Min Postincision	1 Min Poststernotomy	Pericardium Open
HR (beats · min^{-1})									
1	61 ± 4	66 ± 4	78 ± 6	78 ± 5	71 ± 4	73 ± 5	67 ± 4	70 ± 4	74 ± 5
2	65 ± 2	69 ± 2	74* ± 3	77* ± 3	75* ± 3	74* ± 3	69 ± 3	70 ± 3	71 ± 2
MAP (mmHg)									
1	103 ± 4	90* ± 5	94 ± 5	99 ± 6	89* ± 5	90 ± 6	90* ± 5	106 ± 8	87* ± 5
2	101 ± 4	106 ± 3	96 ± 4	98 ± 5	93 ± 3	95 ± 5	96 ± 3	105 ± 5	97 ± 3
CVP (mmHg)									
1	7.9 ± 1.5	4.3 ± 0.8	8.2 ± 0.8	6.8 ± 0.9	6.9 ± 1.0	5.8 ± 0.9	6.4 ± 1.1	6.2 ± 1.2	5.5 ± 0.6
2	6.8 ± 1.3	7.0 ± 1.0	6.3 ± 1.0	5.8 ± 0.7	5.6 ± 0.6	5.2 ± 0.7	6.6 ± 0.6	6.8 ± 0.6	5.6 ± 0.7
PCWP (mmHg)									
1	13.7 ± 1.3	9.0* ± 0.9	11.8 ± 1.1	11.6 ± 1.2	10.2 ± 1.1	10.2 ± 1.4	9.6 ± 1.2	9.8 ± 1.4	10.1 ± 1.1
2	13.2 ± 1.9	14.7 ± 2.7	11.5 ± 1.4	10.6 ± 1.7	9.5 ± 1.3	9.5 ± 1.3	10.2 ± 1.2	12.1 ± 1.9	9.2 ± 1.0
CI (l · min^{-1} · m^{-2})									
1	2.47 ± 0.11	2.42 ± 0.15	2.85 ± 0.19	3.26 ± 0.27	3.02 ± 0.19	2.73 ± 0.20	2.59 ± 0.25	2.47 ± 0.21	2.53 ± 0.20
2	2.83 ± 0.16	2.84 ± 0.14	3.03 ± 0.17	3.08 ± 0.17	3.08 ± 0.17	3.02 ± 0.17	2.75 ± 0.11	2.65 ± 0.12	2.55 ± 0.08
SVRI (dyn · s · cm^{-5} · m^{2})									
1	3,124 ± 163	2,816 ± 148	2,526 ± 254	2,343 ± 183	2,187* ± 74	2,528 ± 179	2,741 ± 236	3,291 ± 217	2,719 ± 174
2	2,757 ± 185	2,873 ± 224	2,422 ± 105	2,419 ± 112	2,307* ± 101	2,417 ± 106	2,626 ± 91	2,995 ± 102	2,902 ± 121
RPP (mmHg · beat · min^{-1} · 10^{-3})									
1	9.51 ± 0.85	9.23 ± 0.89	10.92 ± 1.10	11.85 ± 1.33	9.86 ± 0.80	9.65 ± 1.12	8.88 ± 0.80	10.67 ± 1.18	9.94 ± 0.99
2	9.70 ± 0.57	10.53 ± 0.52	10.31 ± 0.69	10.84 ± 0.79	9.95 ± 0.66	9.76 ± 0.71	9.22 ± 0.55	10.46 ± 0.80	9.63 ± 0.55
DPTI/SPTI									
1	1.12 ± 0.10	1.25 ± 0.09	1.01 ± 0.11	0.94 ± 0.10	0.98 ± 0.09	1.01 ± 0.10	1.20 ± 0.11	1.14 ± 0.09	1.01 ± 0.06
2	0.99 ± 0.08	0.94 ± 0.07	0.85 ± 0.07	0.87 ± 0.08	0.97 ± 0.09	0.92 ± 0.07	1.01 ± 0.05	0.93 ± 0.07	1.01 ± 0.04

Group 1 (iv nitroglycerin), Group 2 (placebo). * $P < 0.006$ *versus* control (Student's *t* test).

To explore the influence of various preoperative variables on the development of intraoperative myocardial ischemia, we divided the patients into those who had developed intraoperative ECG changes of ischemia and those who had not. These groups are compared in table 7. The groups did not differ significantly with respect to age, weight, LVEDP at heart catheterization, ejection fraction, total daily dose of beta-adrenergic blocking agents, fentanyl dose, or volume of iv crystalloid administered prior to cardiopulmonary bypass. The ischemic and nonischemic groups did not differ with respect to the number of coronary artery bypass grafts they received (table 8).

To explore the relationship between hemodynamic variables and ECG changes of myocardial ischemia, we performed an analysis of covariance for repeated measures using the ECG as the covariate. For each hemodynamic datum, the covariate arbitrarily was assigned a value of zero (no ischemia) or one (ischemia) on the basis of the corresponding ECG result from that time period. The analysis determines whether or not a significant correlation exists between the covariate and the hemodynamic variable, and the slope of this relationship is computed. The results are shown on table 9. Heart rate, MAP, and RPP all demonstrated significant positive correlation with the presence of ischemic ECG changes. The DPTI/SPTI ratio was inversely correlated with ECG changes of ischemia. The other variables were not significantly correlated with ischemia.

In a related exercise we compared the eight patients who became ischemic at 1 min postintubation with the 12 patients who were not ischemic at that time, with respect to the hemodynamic changes that occurred between time 2 (preinduction) and intubation. Endotracheal intubation was associated with significantly greater changes in HR, RPP, and DPTI/SPTI in the ischemic compared with the nonischemic patients (table 10).

Discussion

Retrospectively reviewing continuous two-lead ECG recordings from a Holter Monitor®, we detected a 50% incidence of ischemic ECG changes in a group of 20 patients undergoing elective CABG under fentanyl–pancuronium anesthesia. We also noted a significant association between hemodynamic indices of myocardial oxygen demand or balance (HR, MAP, RPP, DPTI/SPTI) and intraoperative ECG changes. Thus, intraoperative ischemic episodes appear to have been precipitated by deteriorating myocardial oxygen balance. The increase in HR observed subsequent to induction of anesthesia may have contributed to the development of myocardial ischemia in the five patients who manifested ECG changes prior to intubation. The stress of intubation

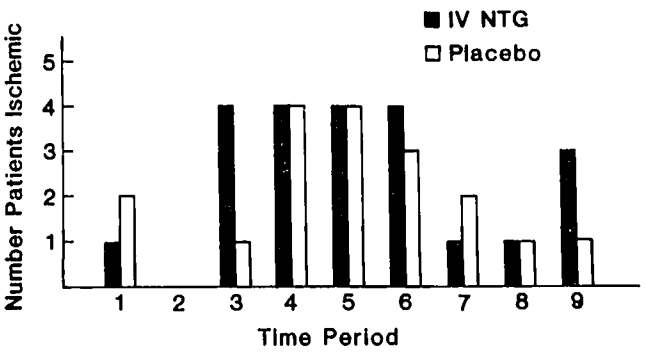

FIG 1. The incidence of ECG changes of myocardial ischemia for Groups 1 (NTG) and 2 (placebo) at the measurement periods listed in Table 1.

appeared to cause a further increase in the incidence of ischemia. The hemodynamic changes at intubation in HR, RPP, and DPTI/SPTI were significantly more severe in the patients who developed ischemia (table 10). The 50 μg/kg fentanyl dose employed was inadequate to prevent a hemodynamic response to surgery in all patients. Twelve patients required supplemental fentanyl during surgery. Although the RPP at sternotomy was not increased significantly with respect to control (table 6), that statistic is falsely reassuring, as five patients developed RPPs exceeding 13×10^3 (range $13.1–16.5 \times 10^3$) 1 min after sternotomy. Using a larger fentanyl dose might have prevented some of these adverse hemodynamic changes.

The increase in HR that occurred with induction and persisted throughout surgery has been observed by other investigators using similar techniques.[14–16] Increases in HR may have been of primary importance in the pathogenesis of myocardial ischemia. A correlation of HR with variables such as RPP and DPTI/SPTI must in part explain the association of these latter variables with ECG changes of ischemia. The observed increase in HR may have been precipitated by the use of pancuronium bromide, an agent with antimuscarinic and sympathomimetic effects, as the muscle relaxant.[17–21] Increases in HR also occur during induction of anesthesia with sufentanil and pancuronium but are absent when metocurine is substituted as the muscle

TABLE 5. Effect of Intravenous Nitroglycerin on the Incidence of Intraoperative ECG Changes of Myocardial Ischemia

	Ischemia	No Ischemia	Total
Group 1	5	4	9
Group 2	5	6	11
Total	10	10	20

Group 1 (iv nitroglycerin), Group 2 (placebo).
The incidence of ischemia does not differ between groups (Fischer's Exact Test).

TABLE 6. Hemodynamic Variables (Mean ± SEM, n = 20)

Time Period	Control	20 min NTG/placebo	25 μg	1 Min Post-intubation	5 Min Post-intubation	50 μg	1 Min Post-incision	1 Min Post-sternotomy	Pericardium open
HR (beats·min^{-1})	63 ± 2	68 ± 2	76* ± 3	77* ± 3	73* ± 3	73* ± 3	68 ± 2	70* ± 2	72* ± 3
MAP (mmHg)	102 ± 3	99 ± 3	96 ± 3	98 ± 4	91* ± 3	93 ± 4	93* ± 3	105 ± 5	93 ± 3
CVP (mmHg)	7.3 ± 1.0	5.8 ± 0.7	7.2 ± 0.7	6.3 ± 0.6	6.2 ± 0.6	5.5 ± 0.5	6.5 ± 0.6	6.5 ± 0.6	5.5 ± 0.4
PCWP (mmHg)	13.4 ± 1.2	12.2 ± 1.6	11.6 ± 0.9	11.0 ± 1.1	9.8* ± 0.8	9.8* ± 1.0	9.9* ± 0.8	11.0 ± 1.2	9.6* ± 0.7
CI (l·min^{-1}·m^{-2})	2.67 ± 0.10	2.66 ± 0.11	2.95 ± 0.13	3.16* ± 0.15	3.06* ± 0.12	2.89 ± 0.13	2.68 ± 0.13	2.57 ± 0.11	2.54 ± 0.10
SVRI (dyn·s·cm^{-5}·m^2)	2,922 ± 129	2,847 ± 137	2,469* ± 125	2,385* ± 101	2,253* ± 65	2,467* ± 98	2,678 ± 114	3,128 ± 114	2,820 ± 102
RPP (mmHg·beat·min^{-1}·10^{-3})	9.61 ± 0.48	9.94 ± 0.50	10.58 ± 0.61	11.29 ± 0.73	9.91 ± 0.50	9.71 ± 0.62	9.06 ± 0.46	10.56 ± 0.67	9.77 ± 0.52
DPTI/SPTI	1.05 ± 0.06	1.08 ± 0.07	0.92 ± 0.06	0.90 ± 0.06	0.97 ± 0.06	0.96 ± 0.06	1.10 ± 0.06	1.02 ± 0.06	1.01 ± 0.03

* $P < 0.006$ *versus* period 1 (Student's *t* test).

relaxant.[22] Because pancuronium blocks reuptake of norepinephrine at sympathetic nerve endings, it has the potential to exacerbate sympathomimetic effects caused by other mechanisms. We believe the use of pancuronium contributed substantially to the pathogenesis of myocardial ischemia in this study.

Several additional factors besides pancuronium theoretically may cause increases in heart rate and myocardial oxygen demand during induction of anesthesia with fentanyl and pancuronium. These include hypercapnia related to fentanyl induced muscle rigidity,[6,23] indirect sympathomimetic effects of fentanyl,[24,25] and awareness in paralyzed patients. Our experimental protocol did not allow an evaluation of the contribution of these factors to the hemodynamic changes we observed.

Inadequate beta-adrenergic blockade has been postulated as an explanation of adverse hemodynamic responses during fentanyl–pancuronium anesthesia.[26] We discontinued beta-blockers approximately 10 hr preoperatively. Continuing these medications up to the time of surgery might have altered our results. We could not differentiate between the ischemic and nonischemic patients in our study on the basis of daily maintenance dose of propranolol. However, this does not rule out a difference in the level of beta-adrenergic blockade.[27]

Other investigators have observed adverse hemodynamic changes during CABG under fentanyl–pancuronium anesthesia,[5,6] but a high incidence of ischemic ECG changes previously has not been reported. However, metabolic evidence of myocardial ischemia manifested as myocardial lactate production was reported in seven of nine patients studied by Sonntag *et al.*[7] Upon first consideration, the 50% incidence of intraoperative myocardial ischemia in our study seems excessive, but this incidence is not high when compared with similar studies of patients with CAD, where objective evidence of intraoperative myocardial ischemia was sought intensively by continuous ECG monitoring[11,28] or measurement of myocardial lactate production.[7,29] The Holter Monitor® provides a continuous two-lead ECG recording on electromagnetic tape and accurate ST segment reproduction.[30,31] Thus, we were able to make a careful search for ST segment changes in all complexes that were not interfered with by electrocautery. The battery-operated feature of the Holter Monitor® eliminates 60-Hz interference emanating from other electronic equipment in the cardiovascular operating room.

We noted a positive correlation between ischemic ECG changes and indices of myocardial oxygen demand (HR, MAP, RPP).[32] In addition, a significant negative correlation was noted between ischemia and DPTI/SPTI, an index of myocardial oxygen balance.[33] Our data support the continued use of such indices as part of the intraoperative evaluation of patients with coronary

artery disease who undergo narcotic–relaxant anesthesia. It should be remembered that although a general correlation exists within a population, indices of ischemia may be misleading in individual patients. For example, if critical values for the RPP and DPTI/SPTI had been established at $>9.5 \times 10^3$ and <1.00, respectively, then at the time of intubation each index would have identified seven of eight (87.5%) ischemic patients. However, frequent false-positive results reduce the overall specificity of the indices to 65–70% at the same time period. The indices still have value to the extent that sensitivity may be more important than specificity in this situation.

The absence of a significant positive correlation between ECG changes of ischemia and the PCWP was noteable in our data. Kaplan and Wells have suggested that PCWP wave-form abnormalities may be sensitive indicators of myocardial ischemia and precede ECG changes.[34] Our data, and that of others, suggest that this is not always the case. At the time of onset of ECG changes, of nine ischemic patients in our study for whom we had good fidelity PCWP tracings, only two fulfilled the criteria for ischemia of Kaplan and Wells (ac-wave > 15 mmHg or v-wave > 20 mmHg). Similarly, the data of Sonntag *et al.* do not indicate that PCWP increases accompanied myocardial lactate production in their patients.[7] The pathogenesis of myocardial ischemia may determine whether or not PCWP increase occurs. In patients with CAD, angina induced by exercise is associated with an increased LVEDP, whereas that induced by atrial pacing is not.[35] During pacing-induced angina, venous return and cardiac output are unchanged and a decrease in stroke volume must accompany the increase in HR.[35] Thus, LVEDP does not increase, although the relationship between LVEDP and LVSWI may reveal left ventricular dysfunction.[36,37] During exercise-induced angina, venous return is increased and HR relatively lower, so that LVEDP increases. Significantly, in Kaplan and Wells' study, patients who had ECG changes of ischemia in the absence of PCWP abnormalities had significantly faster heart rates than those with both ECG and PCWP abnormalities. Thus, during fentanyl–pancuronium anesthesia, where HR increases are important in the pathogenesis of ischemia, PCWP increase may be an unreliable indicator of ischemia.

Prior to induction of anesthesia, continuous 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ iv NTG infusion produced significant decreases in MAP and PCWP that did not occur with placebo. However, no sustained hemodynamic differences between Groups 1 and 2 were apparent over the entire study period. In the absence of a significant intergroup difference in hemodynamics, iv NTG was not superior to placebo infusion for the prevention of myocardial ischemia. This finding supports the hypothesis that, in the absence of coronary artery spasm, beneficial effects of NTG in myocardial ischemia are related to changes in systemic hemodynamics[9,38] rather than to coronary vasodilation.[39] Systemic administration of NTG does produce a significant increase in the RPP at which angina occurs in patients with CAD.[40,41] However, this increase is only of the order of 9–12%. Thus, it is not surprising that patients in our study who developed ischemia in relation to large RPP increases were not protected by NTG infusion.

Despite randomization, patients in Group 1 received significantly more coronary bypass grafts than those in Group 2. This suggests a bias toward a higher incidence of ischemia in Group 1, possibly invalidating the conclusion that iv NTG was ineffective in preventing ischemia. However, the ischemic and nonischemic patients did not differ significantly with respect to the number of bypass grafts they received (table 8), demonstrating that the number of grafts required was not an important factor in the pathogenesis of intraoperative ischemia. Ischemia appears to have been precipitated by adverse hemodynamic changes and not related to differences in underlying coronary pathology.

We do not feel that our results preclude the possibility that prophylactic NTG infusion might prove useful during fentanyl–pancuronium anesthesia if a different experimental protocol were followed. We believe the

TABLE 7. Preoperative Characteristics and Intraoperative Management Variables for Ischemic (n = 10) and Nonischemic (n = 10) Groups (Mean ± SEM)

	Ischemic	Nonischemic
Age (yr)	54.4 ± 2.9	56.1 ± 2.9
Weight (kg)	82.2 ± 2.6	83.4 ± 3.2
LVEDP at heart catheterization (mmHg)	15.0 ± 1.1	16.5 ± 1.3
Ejection fraction	0.58 ± 0.04	0.66 ± 0.05
Daily propranolol dose (mg/day)	152 ± 14	207 ± 52
Total dose fentanyl (μg/kg)	55 ± 2	55 ± 2
Total crystalloid prebypass (l)	1.1 ± 0.1	1.0 ± 0.2

Ischemic (ischemic ECG changes intraoperatively).
Nonischemic (no ECG changes).
No significant differences existed between groups.

TABLE 8. Number of Coronary Bypass Grafts Received by Patients with and without ECG Changes of Myocardial Ischemia

	Number of Grafts					
	1	2	3	4	5	Total
Ischemia	1	3	4	1	1	10
No ischemia	2	1	3	3	1	10

The ischemic and nonischemic groups do not differ significantly with respect to the number of coronary bypass grafts (Wilcoxon–Mann–Whitney rank sums test).

TABLE 9. Analysis of Covariance Relating Hemodynamic Variables to ECG Changes of Ischemia

	Slope of Regression
HR (beats · min^{-1})	7.58*
MAP (mmHg)	5.61†
CVP (mmHg)	ns
PCWP (mmHg)	ns
CI (l · min^{-1} · m^{-2})	ns
SVRI (dyn · s · cm^{-5} · m^2)	ns
RPP (mmHg · beats · min^{-1} · 10^{-3})	1.96*
DPTI/SPTI	−0.14*

* $P < 0.001$.
† $P < 0.05$.
ns = not significant. See text for details.

dose of iv NTG administered approached the maximum safe dose that can be administered to awake premedicated patients with CAD, without concurrent fluid supplementation. In a pilot study,[42] we encountered problems with hypotension, tachycardia, and very low cardiac filling pressures when a dose of 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of iv NTG was utilized. However, the use of a larger iv NTG dose with fluid supplementation might have been protective.

TABLE 10. Hemodynamics at Intubation for Ischemic (n = 8) and Nonischemic (n = 12) Patients

	Preinduction	1/min Postintubation
HR (beats · min^{-1})		
Isch.	65 ± 4	82 ± 4*
NIsch.	69 ± 3	74 ± 4
MAP (mmHg)		
Isch.	101 ± 6	107 ± 6
NIsch.	97 ± 4	92 ± 4
CVP (mmHg)		
Isch.	6.7 ± 0.9	8.0 ± 0.9
NIsch.	5.1 ± 1.0	5.1 ± 0.5
PCWP (mmHg)		
Isch.	15.3 ± 3.3	13.9 ± 1.8
NIsch.	10.0 ± 1.4	9.1 ± 1.0
CI (l · min^{-1} · m^{-2})		
Isch.	2.86 ± 0.16	3.65 ± 0.20
NIsch.	2.52 ± 0.14	2.84 ± 0.15
SVRI (dyn · s · cm^{-5} · m^{-2})		
Isch.	2.65 ± 0.15	2.20 ± 0.14
NIsch.	2.98 ± 0.20	2.53 ± 0.14
RPP (mmHg · beats · min^{-1} · 10^{-3})		
Isch.	9.56 ± 0.85	13.2 ± 1.3*
NIsch.	10.2 ± 0.6	9.97 ± 0.63
DPTI/SPTI		
Isch.	1.09 ± 0.11	0.77 ± 0.07*
NIsch.	1.07 ± 0.09	0.99 ± 0.08

Isch = ischemic (n = 8) at l/min postintubation; NIsch = nonischemic (n = 12) at l/min postintubation.
* $P < 0.05$ change from preinduction, Isch. *vs.* NIsch.

In a nonrandomized, nonplacebo controlled study, Coriat *et al.*[11] found that prophylactic iv NTG infusion (0.91 $\mu g \cdot kg^{-1} \cdot min^{-1}$ administered through an unspecified delivery system) with fluid supplementation was effective in preventing perioperative ECG changes of ischemia in patients with angina undergoing "balanced anesthesia" with thiopental, succinylcholine, low-dose fentanyl, nitrous oxide, and pancuronium. An extremely sensitive definition of ischemia was used (ST depression lasting for 1 s). Invasive monitoring was not used, but ischemia appeared to be related to episodes of hypertension. Perhaps NTG is more effective when hypertension rather than tachycardia is the most significant factor in the pathogenesis of ischemia. Otherwise, we cannot explain the marked difference between the results of Coriat *et al.* and our own.

In conclusion, we have demonstrated a 50% incidence of intraoperative ECG changes of myocardial ischemia during fentanyl–pancuronium anesthesia for CABG. Changes in HR, RPP, and DPTI/SPTI were associated with myocardial ischemia, but PCWP increase was not. A continuous 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ iv NTG infusion was no more effective than placebo in preventing myocardial ischemia.

The authors thank Maureen Cumming, R.N., for technical assistance; Anne Cameron and Karen Morin for typing the manuscript; Cindy Wong for statistical analysis; Dr. A. Morris, B. Falk, RCT, and N. Thomas, RCT, for Holter Monitor® analysis; and Drs. M. Cohen, J. Barwinsky, J. Teskey, S. Bhattacharya, S. Kim, M. Crocker, and J. Scatliff for their patience and cooperation.

References

1. Waller JL, Kaplan JA, Jones EL: Anesthesia for coronary revascularization, Cardiac Anesthesia. Edited by Kaplan JA. New York, Grune and Stratton, 1979, pp 241–280
2. Stanley TH, Philbin DM, Coggins CH: Fentanyl–oxygen anesthesia for coronary artery surgery: Cardiovascular and antidiuretic hormone responses. Can Anaesth Soc J 26:168–171, 1979
3. Stanley TH, Berman L, Green O, Robertson D: Plasma catecholamine and cortisol responses to fentanyl–oxygen anesthesia for coronary-artery operations. ANESTHESIOLOGY 53:250–253, 1980
4. Quinton L, Whalley DG, Wynands JE, Morin JE, Burke J: High dose fentanyl anesthesia with oxygen for aorto-coronary bypass surgery. Can Anaesth Soc J 28:314–320, 1981
5. Edde RR: Hemodynamic changes prior to and after sternotomy in patients anesthetized with high-dose fentanyl. ANESTHESIOLOGY 55:444–446, 1981
6. Waller JL, Hug CC, Nagle DM, Craver JM: Hemodynamic changes during fentanyl–oxygen anesthesia for aortocoronary bypass operation. ANESTHESIOLOGY 55:212–217, 1981
7. Sonntag H, Larsen R, Hilfiker O, Kettler D, Brockschnieder B: Myocardial blood flow and oxygen consumption during high-

dose fentanyl anesthesia in patients with coronary artery disease. ANESTHESIOLOGY 56:417–422, 1982
8. Abrams J: Nitroglycerin and long-acting nitrates. N Engl J Med 302:1234–1237, 1980
9. Feldman RL, Conti CR: Relief of myocardial ischemia with nitroglycerin: What is the mechanism? Circulation 64:1098–1100, 1981
10. Kaplan JA, Dunbar RW, Jones EL: Nitroglycerin infusion during coronary-artery surgery. ANESTHESIOLOGY 45:14–21, 1976
11. Coriat P, Fusciardi J, Daloz M, Harari A, Ducardonet A, Viars P: Prévention de l'ischémie myocardique peropératoire: Emploi d'une perfusion continue de trinitrine. Ann Fr Anesth Reanim 1:47–51, 1982
12. Buckberg GD, Towers B, Paglia DE, Mulder DG, Maloney JV: Subendocardial ischemia after cardiopulmonary bypass. J Thorac Cardiovasc Surg 64:669–680, 1972
13. Winer BJ. Statistical Principles in Experimental Design. New York, McGraw-Hill, 1981, pp 796–809
14. Sprigge JS, Wynands JE, Whalley DG, Bevan DR, Townsend GE, Nathan H, Patel YC, Srikant CB: Fentanyl infusion anesthesia for aortocoronary bypass surgery: Plasma levels and hemodynamic response. Anesth Analg 61:972–978, 1982
15. Wynands JE, Wong P, Whalley DG, Sprigge JS, Townsend GE, Patel YC: Oxygen–fentanyl anesthesia in patients with poor ventricular function: Hemodynamics and plasma fentanyl concentrations. Anesth Analg 62:476–482, 1983
16. Kentor ML, Schwalb AJ, Lieberman RW: Rapid high dose fentanyl induction for CABG. ANESTHESIOLOGY 53:S95, 1980
17. Stoelting RK: The hemodynamic effects of pancuronium and *d*-tubocurarine in anesthetized patients. ANESTHESIOLOGY 36:612–615, 1972
18. Stanley TH, Liu WS: Cardiovascular effects of meperidine–N_2O anesthesia before and after pancuronium. Anesth Analg 56:669–673, 1977
19. Booij LHDJ, Edwards RP, Sohn YJ, Miller RD: Cardiovascular and neuromuscular effects of Org NC 45, pancuronium, metocurine and *d*-tubocurarine in dogs. Anesth Analg 59:26–30, 1980
20. Domenech JS, Garcia RC, Sasiain JMR, Loyola AQ, Oroz JS: Pancuronium bromide: An indirect sympathomimetic agent. Br J Anaesth 48:1143–1148, 1976
21. Marshall RJ, McGrath JC, Miller RD, Docherty JR, Lamar JC: Comparison of the cardiovascular actions of Org NC 45 with those produced by other non-depolarizing neuromuscular blocking agents in experimental animals. Br J Anaesth 52:21S–31S, 1980
22. Khoury GF, Estafanous FG, Zurick AM, Lytle B: Sufentanil/pancuronium vs sufentanil/metocurine anesthesia for coronary artery surgery. ANESTHESIOLOGY 57:A47, 1982
23. Comstock MK, Scamman FL, Carter JG, Moyers JR, Stevens WC: Rigidity and hypercarbia on fentanyl-oxygen induction. ANESTHESIOLOGY 51:S28, 1979
24. Rorie DK, Muldoon SM, Tyce GM: Effects of fentanyl on adrenergic function in canine coronary arteries. Anesth Analg 60:21–27, 1981
25. Hicks HC, Mowbray AG, Yhap EO: Cardiovascular effects of and catecholamine responses to high dose fentanyl-O_2 for induction of anesthesia in patients with ischemic coronary artery disease. Anesth Analg 60:563–568, 1981
26. deLange S, Boscoe MJ, Stanley TH, Pace N: Comparison of sufentanil-O_2 and fentanyl-O_2 for coronary artery surgery. ANESTHESIOLOGY 56:112–118, 1982
27. Nies AS, Shand DG: Clinical pharmacology of propranolol. Circulation 52:6–14, 1975
28. Roy WL, Edelist G, Gilbert B: Myocardial ischemia during noncardiac surgical procedures in patients with coronary-artery disease. ANESTHESIOLOGY 51:393–397, 1979
29. Wilkinson PL, Hamilton WK, Moyers JR, Graham BG, Ports TA, Ullyot DJ, Chatterjee K: Halothane and morphine–nitrous oxide anesthesia in patients undergoing coronary artery bypass operation: Patterns of intraoperative ischemia. J Thorac Cardiovasc Surg 82:372–382, 1981
30. Stern S, Tzivoni D: The reliability of the Holter–Avionics system in reproducing the ST-T segment. Am Heart J 84:427–429, 1972
31. Stern S, Tzivoni D, Stern Z: Diagnostic accuracy of ambulatory ECG monitoring in ischemic heart disease. Circulation 52:1045–1049, 1975
32. Barash PG, Kopriva CJ: The rate-pressure product in clinical anesthesia: Boon or bane? Anesth Analg 59:229–231, 1980
33. Hoffman JIE: Determinants and prediction of transmural myocardial perfusion. Circulation 58:381–391, 1978
34. Kaplan JA, Wells PH: Early diagnosis of myocardial ischemia using the pulmonary arterial catheter. Anesth Analg 60:789–793, 1981
35. O'Brien KP, Higgs LM, Glancey LK, Epstein SE: Hemodynamic accompaniments of angina: A comparison during angina induced by exercise and by atrial pacing. Circulation 39:735–743, 1969
36. Parker JO, Ledwich JR, West RO, Case RB: Reversible cardiac failure during angina pectoris: Hemodynamic effects of atrial pacing in coronary artery disease. Circulation 39:745–757, 1969
37. Linhart JW, Hildner FJ, Barold SS, Lister JW, Samet P: Left heart hemodynamics during angina pectoris induced by atrial pacing. Circulation 40:483–492, 1969
38. Ganz W, Marcus HS: Failure of intracoronary nitroglycerin to alleviate pacing-induced angina. Circulation 46:880, 1972
39. Brown BG, Bolson E, Peterson RB, Pierce CD, Dodge HT: The mechanisms of nitroglycerin action: Stenosis vasodilation as a major component of the drug response. Circulation 64:1089–1097, 1981
40. Detry JMR, Bruce RA: Effects of nitroglycerin on "maximal" oxygen intake and exercise electrocardiogram in coronary heart disease. Circulation 43:155–163, 1971
41. Kimchi A, Lee G, Amsterdam E, Fujii K, Krieg P, Mason DT: Increased exercise tolerance after nitroglycerin oral spray: A new and effective therapeutic modality in angina pectoris. Circulation 67:124–127, 1983
42. Mutch WAC, Culligan JD, Cote DD, Thomson IR: Hemodynamic effects of intravenous nitroglycerin: Importance of the delivery system. Anesth Analg 61:927–932, 1982