Anesthesiology
61:193–196, 1984

Ronald D. Miller, M.D., Editor

Prevention of Intraoperative Myocardial Ischemia during Noncardiac Surgery with Intravenous Nitroglycerin

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When the heart is subjected to stressful situations, (*e.g.*, endotracheal intubation), an imbalance between myocardial oxygen supply and demand may cause myocardial ischemia in patients suffering from coronary artery disease.[1] Although fentanyl-N_2O-pancuronium anesthesia has the apparent advantage of preventing cardiovascular stimulation during endotracheal intubation and surgery,[2] the incidence of intraoperative myocardial ischemia with this approach has not been determined.

The beneficial effects of iv administered nitroglycerin (NTG) have been documented in ischemic heart disease.[3,4] Perhaps iv NTG would optimize myocardial oxygenation during surgery and minimize the risk of intraoperative myocardial ischemia. We employed a randomized study to compare the incidence of intraoperative ischemic episodes in patients with angina pectoris undergoing noncardiac surgery during fentanyl-N_2O-pancuronium anesthesia with prophylactic iv NTG infusion administered at the dose of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

MATERIAL AND METHODS

Forty-five patients undergoing noncardiac surgery were studied with a clear history of stable effort-related angina pectoris, which provoked slight or marked limitation of physical activity Class II or III of the Canadian Cardiovascular Society.[5] All patients chronically were treated for their symptoms and were receiving long-acting nitrates. Patients who previously had undergone coronary bypass surgery were not studied. None of the patients had congestive heart failure with dyspnea. We excluded patients with left bundle branch block and left ventricular hypertrophy with strain pattern, all of which render interpretation of the ST segment difficult. Informed consent was obtained from each patient at the preoperative visit, and the protocol was approved by the Ethics Committee of our institution. The patients randomly were assigned to NTG 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (Group 1 n = 22) or 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (Group 2 n = 23).

Both groups were identical in age (68 ± 8 *vs.* 66 ± 7), infarction dating for more than 6 months (18 *vs.* 15), and grade of angina (marked limitation of activity: 14 *vs.* 12). The type of operation was similar in both groups (carotid stenosis: 12 *vs.* 13; aortobifemoral bypass grafting: 5 *vs.* 6; axillary femoral bypass: 1 *vs.* 1; lumbar sympathectomy: 1 *vs.* 2; colectomy: 3 *vs.* 1). Other than nitrates, antianginal drugs being taken were short-acting beta-blockers—7 *versus* 9; long-acting beta-blockers—3 *versus* 2; amiodarone—6 *versus* 4; calcium channel blockers—7 *versus* 10.

Organic nitrates, beta-adrenergic receptor blockers and antihypertensive medications (clonidine and methyldopa) were withheld from midnight of the evening prior to surgery. Preinduction heart rate and blood pressure did not differ in the two groups (table 1). Anesthetic procedure was identical in both groups.

Each patient was premedicated with flunitrazepam (0.02 mg/kg) and atropine (0.005 mg/kg) im 90 min before anesthesia. Upon arrival in the operative room, electrocardiographic electrodes were applied and 300 ml of crystalloid infused iv in ten min. The iv NTG infusion was started at the concentration of 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The infusion was increased every 3 min at the rate of 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to obtain a dose of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in Group 1 and 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in the patients of Group 2.

Any decrease in arterial blood pressure of more than 20% or increase in heart rate greater than 20% in relation to initial values led the anesthetist to infuse colloids iv. Ten minutes after having reached the determined dose, anesthesia was induced with flunitrazepam–(0.02 mg/kg) fentanyl (6 $\mu g \cdot kg^{-1}$) slowly administered iv while the patient breathed 100% oxygen. Respirations were assisted at first and then controlled with 60% N_2O and oxygen. When patients were unresponsive, pancuronium (0.08 $mg \cdot kg^{-1}$) was administered iv and the trachea intubated. During surgery, fluids were infused at the discretion of the anesthetist. Additional fentanyl was injected when

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Received from the Department of Anesthesiology, Hôpital de la Pitié, 75013 Paris, France. Accepted for publication December 19, 1983.

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Key words: Anesthetics: fentanyl; N_2O; pancuronium. Heart: myocardial ischemia; nitroglycerin. Monitoring: Holter method. Surgery: Noncardiac surgery.

TABLE 1. Cardiovascular Responses to iv NTG Infusion (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ = Group 1; 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ = Group 2) during Fentanyl N_2O Pancuronium Anesthesia

	Control (1)	NTG Infusion (2)	Tracheal Intubation (3)	After Controlled Ventilation (4)	Skin Incision (5)
Systolic blood pressure (mmHg)					
Group 1	148 ± 17	138 ± 22	140 ± 32	120 ± 24*	125 ± 23
Group 2	157 ± 24	118 ± 22*	147 ± 26	107 ± 18†	115 ± 19
Diastolic blood pressure (mmHg)					
Group 1	80 ± 6	77 ± 7	76 ± 7	62 ± 8*	69 ± 9
Group 2	88 ± 12	75 ± 10*	74 ± 11	70.2 ± 8†	76 ± 8
Heart rate (beats · min)					
Group 1	81 ± 10	84 ± 11	85 ± 12	86 ± 12	87 ± 12
Group 2	77 ± 10	80 ± 11	82 ± 10	82 ± 12	83 ± 13

Systolic blood pressure. Group 1: * = $P < 0.001$ 4 *versus* 1, 2, 3; Group 2: * = $P < 0.001$ 2 *versus* 1; † = $P < 0.05$ 4 *versus* 2.

Diastolic blood pressure group 1: * = $P < 0.001$ 4 *versus* 1, 2, 3; Group 2: * = $P < 0.001$ 2 *versus* 1; † = $P < 0.02$ 4 *versus* 2.

clinically warranted, principally to treat hypertension and tachycardia in response to surgery. Ventilation was controlled throughout anesthesia. Postoperatively patients were warmed while being sedated if necessary with fentanyl in a recovery room and the trachea only extubated when their temperature was normal (36.5° C). The rate of NTG infusion was decreased progressively while verifying the oscilloscopic ECG 2 h after extubation of the trachea.

Heart rate, systolic and diastolic blood pressure, measured by sphygmomanometry at 1) control pre NTG infusion; 2) 5 min after NTG infusion; 3) intubation of the trachea; 4) at the beginning of controlled ventilation; 5) 1 min after skin incision; 6) 15 min after skin incision, were compared in the two groups.

In 11 patients in whom the surgery was an aorto-bifemoral bypass grafting, a radial artery and pulmonary artery catheter were inserted after induction of anesthesia. During the infrarenal cross clamping and unclamping, the pulmonary capillary wedge pressure was maintained between 10 and 20 mmHg with infusion of crystalloid iv or increasing, if necessary, the TNT infusion.

The long-term ECG recording[6] was started just before arrival in the operating room for 24 h. Lead CM5 and D2 were recorded. An ischemic episode was defined as when an ischemic-type ST segment depression greater than 1 mm was present for more than 10 beats in either lead. The occurrence of premature ventricular beats was noted. The reviewer of the recorded material was well versed in the Holter technique and interpretation of ST segment depression. The Holter monitor tapes were examined retrospectively and blindly. A digital clock synchronized to the recorded tape permitted accurate time marking. The patients' charts were examined retrospectively to determine in which situations myocardial ischemia occurred.

The long-term ECG recording gives a retrospective indication of myocardial ischemia. Therefore, a good ocilloscopic trace (lead V5) was monitored during the intervention and the postoperative period. When an ischemic-type ST segment depression persisted, the dose of NTG was increased to 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in the patients in Group 1.

Statistical analysis was performed with the *t* test and the chi-square test.

RESULTS

No patient exhibited ischemic episodes before induction of anesthesia. Continuous monitoring of the ECG revealed ischemic-type ST segment depression in 14 out of 22 patients in Group 1. In seven patients, the ischemic episodes were detected by the anesthetist on the oscilloscopic trace monitored during surgery. In one case the depression disappeared after fentanyl administration but it reappeared later during surgery and regressed when NTG was increased to 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In the six other cases the ST segment depression regressed when NTG was increased and maintained at 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and did not reappear. In these seven patients the ECG recording confirmed the ST segment depression. These patients were considered as part of Group 1 since their ST segment depression occurred when NTG was administered at the dose of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. ST segment depressions were not detected during surgery in seven patients. These depressions all lasted for more than 5 min and were observed more than once in three patients. Eighteen ischemic episodes were noted in 14 patients in Group 1. These episodes started during induction in four cases, following skin incision in four cases, during the surgical procedure in eight cases, and during the warming-up period in two cases. Six out of 18 episodes of myocardial ischemia were associated with an increase of more than 20% in both blood pressure and heart rate; seven others were associated with an increase of more than 20% in heart rate.

In Group 2 ischemic ST segment depressions were

observed in only four out of 23 patients. These depressions started more than 30 min after skin incision, one of them associated with an increase (20%) in both heart rate and blood pressure and one other associated with an increase (20%) in heart rate. In one case this was detected during the surgical procedure and was corrected with fentanyl administration. In both groups no ST segment depression appeared isolated in lead II, 85% were noted only in lead V5, and 15% were noted in both leads. The incidence of myocardial ischemia is significantly lower in Group 2 ($P < 0.002$: chi-square test). After termination of the NTG infusion, two patients in Group 1 and one patient in Group 2 had ST segment depression. These three patients had presented episodes of myocardial ischemia during surgical procedure.

The occurrence of more than five premature ventricular beats during 1 min was noted in six patients in Group 1 and in three patients in Group 2.

Both groups received 300 ml of crystalloids before iv NTG. However, patients in Group 2 received more iv colloids (619 ± 174 ml) than those in Group 1 (313 ± 114 ml) ($P < 0.001$).

There was no difference in heart rate and blood pressure in Groups 1 and 2 between the control values and during endotracheal intubation (table 1). At the beginning of controlled ventilation and at skin incision, systolic blood pressure was slightly but significantly ($P < 0.02$) lower in Group 2 than in Group 1. There was no difference in diastolic blood pressure between these two groups. During intubation of the trachea in six patients of Group 1 and four of Group 2 and during the surgical procedure in six patients of Group 1 and in two of Group 2, systolic blood pressure increased more than 20% in relation to the control preinduction value.

In patients undergoing aorto–femoral bypass, no ST segment depression was noted during clamping or unclamping, but the NTG doses had been modified during these periods in both groups to maintain an adequate pulmonary capillary wedge pressure. All patients had no problems postoperatively. There were no intraoperative myocardial infarctions. In patients with preoperative positive T waves, 5 of 13 patients in Group 1 (three with myocardial ischemia) and in 2 of 10 patients in Group 2 with myocardial ischemia had negative T-waves appearing in the postoperative ECG.

Discussion

The prevention of myocardial ischemia is the principal concern of the anesthetist during surgical procedures in patients suffering from angina pectoris. Effectively, myocardial ischemia has not only immediate deleterious effects but also induces prolonged postischemic ventricular dysfunction.[7] The aim of our study was to define the dose of NTG that would prevent myocardial ischemia during noncardiac surgical procedures. Intravenous NTG infusion was tested in this study, because it is an effective antianginal medication[3] and can be administered iv safely during surgery.[8]

All the patients studied were suffering from angina and received chronic administration of long-acting nitrates. We preferred to administer iv NTG at small doses to the patients in Group 1 instead of administering oral long-acting nitrates a few hours before surgery.

We used the continuous monitoring of the electrocardiogram by the Holter method, which provides a good opportunity for detecting episodes of myocardial ischemia during the operative period. The method of scanning superimposes each QRS complex on the immediately preceding complex plus the variations in QRS-T become readily apparent.[6] Lead V5 and D2 were monitored since some 89% of the ST segment information obtained in the conventional 12 leads exercise electrocardiogram are found in lead V5.[9] In our study, no ST segment depression appeared isolated in lead D2.

For NTG to improve regional myocardial blood supply and oxygen demand, sufficient blood levels have to be achieved during NTG infusion. When NTG infusion is administered during fentanyl-O_2-pancuronium anesthesia at a rate of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, its hemodynamic effects seem to be reversed by iv crystalloid administration and induction of anesthesia and the prevention of intraoperative myocardial ischemia is not obtained.[10] Moreover, small coronary vessels only dilate in response to either much higher nitrate concentrations or to intracoronary injection.[4]

Thus, we compare the effectiveness of iv NTG infusion administered at a dose of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (Group 1) and 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (Group 2) in preventing intraoperative myocardial ischemia in patients with angina pectoris undergoing noncardiac surgical procedures. The continuous monitoring of the ECG revealed a high incidence (14/22) of intraoperative myocardial ischemia in Group 1. Although fentanyl-N_2O-pancuronium anesthesia procures hemodynamic stability before operation and lack of cardiovascular stimulation following endotracheal intubation and surgical stimulation,[2] this anesthetic did not prevent effectively the occurrence of intraoperative myocardial ischemia in patients suffering from angina pectoris. Our findings agree with those of Mutch *et al.*,[10] who demonstrated that prophylactic iv NTG infusion (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) does not decrease the incidence of myocardial ischemia during fentanyl-O_2-pancuronium anesthesia in patients undergoing coronary artery bypass grafting. However, when ST segment depression was detected intraoperatively on the oscilloscopic trace, the NTG infusion was increased to 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$, which led to the improvement of ST segment depression.

The significantly lower frequency of ischemic ST seg-

ment depression observed in the patients receiving iv NTG infusion at a dose of 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (Group 2) suggests that NTG is highly effective in preventing intraoperative myocardial ischemia in patients with angina pectoris only at this dose. The mechanism responsible for the beneficial effects of iv NTG administered at the dose of 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ cannot be determined by the findings of the present study. Nitrates have both direct effects on the coronary artery and indirect effects on the heart secondary to their general systemic action.[3] The latter mechanism generally is considered as predominant.[4] The nitrate-induced reduction in venous tone, which has beneficial effects on both oxygen supply and demand, probably was not a factor in view of the large iv fluid infusion administered to prevent reflex tachycardia. Because of our concern that reflex tachycardia may have masked the potentially beneficial effects of NTG, large iv fluid infusion was instituted when NTG infusion was started. Heart rate was unchanged in both groups, but the iv fluid administration was significantly greater in Group 2.

No significant reduction in systolic and diastolic blood pressure was noted between the two groups during intubation of the trachea; however, blood pressure was decreased modestly but significantly during skin incision in Group 2. Fewer patients in Group 2 showed increase in systolic blood pressure of more than 20% in relation to the pressure noted at the control time. This lower blood pressure noted in Group 2 could reduce myocardial oxygen consumption.

The efficiency of NTG in preventing intraoperative myocardial ischemia also may be related to an improvement in myocardial oxygen supply in the jeopardized myocardium. Abnormalities in left ventricular regional function caused by exercise in patients with coronary artery disease are mitigated by prophylactic NTG[11] and the coronary flow in the subendocardial vessel is improved.[12] The direct action of NTG on coronary arteries when administered at sufficient doses appears to be a real component of the beneficial effects of the drug.[13] Nitrates can relieve spasms, induce dilation of collateral and increase coronary collateral flow,[14] and provoke a vasodilation of epicardial coronary stenoses.[15]

In summary, we found that the continuous monitoring of the ECG used in this study revealed a high incidence of intraoperative myocardial ischemia in patients suffering from coronary artery disease during noncardiac surgical procedures, despite continuous administration of NTG at a dose of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. On the other hand, NTG, when administered at a dose of 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$, is highly effective in preventing intraoperative ischemic episodes. Apparently the lower incidence of intraoperative myocardial ischemia in Group 2 was related to the higher infusion rate of NTG. Although we inherently believe that decreasing the incidence of intraoperative myocardial ischemic episodes is essential, no patient in either group suffered a myocardial infarction either intraoperatively or postoperatively.

References

1. Coriat P, Harari A, Daloz M: Clinical predictors of intraoperative myocardial ischemia in patients with coronary artery disease undergoing non-cardiac surgery. Acta Anaesth Scand 26:287–290, 1982
2. Bennett GR, Stanley TH: Human cardiovascular responses to endotracheal intubation during morphine-N_2O and fentanyl-N_2O anesthesia. ANESTHESIOLOGY 52:520–522, 1980
3. Abrams J: Nitroglycerin and long-acting nitrates. N Engl J Med 302:1234–1237, 1980
4. McGregor M: The nitrates and myocardial ischemia. Circulation 66:689–692, 1982
5. Campeau L: Grading of angina pectoris. Circulation 54:522–523, 1976
6. Bragg-Remschell DA, Anderson CM, Winkle RA: Frequency response characteristics of ambulatory ECG monitoring systems and their implications for ST segment analysis. Am Heart J 103:20–31, 1982
7. Braunwald E, Kloner RA: The stunned myocardium: prolonged, postischemic ventricular dysfunction. Circulation 66:1146–1149, 1982
8. Kaplan JA, Dunbar RW, Jones EL: Nitroglycerin infusion during coronary artery surgery. ANESTHESIOLOGY 45:14–21, 1976
9. Blackburn H, Taylor HL, Okamoto N: Standardization of the exercise electrocardiogram. A systematic comparison of chest lead configurations employed for monitoring during exercise, Physical Activity and the Heart. Edited by Maroven M, Barry AJ. Springfield, Charles C Thomas. pp 101–133, 1966
10. Mutch WAC, Culligan JD, Thomson IR: Prevention of intraoperative myocardial ischemia: A randomized trial of intravenous nitroglycerin *vs.* placebo. ANESTHESIOLOGY 57:S52, 1982
11. Borer J, Bacharach S, Green M: Effect of nitroglycerin on exercise-induced abnormalities of left ventricular regional function and ejection fraction in coronary artery disease. Circulation 57:314–320, 1978
12. Cohn PF, Maddox D, Holman BL: Effect of sublingually administered nitroglycerin on regional myocardial blood flow in patients with coronary artery disease. Am J Cardiol 39:672–678, 1977
13. Feldman RL, Conti CR: Editorial: Relief of myocardial ischemia with nitroglycerin: What is the mechanism? Circulation. 64:1098–1100, 1981
14. Fam WM, McGregor M: Effect of coronary vasodilator drugs on retrograde flow in areas of chronic myocardial ischemia. Circ Res 15:355–365, 1964
15. Brown BG, Bolson E, Peterson RB: The mechanism of nitroglycerin: stenosis of vasodilation as a major component of the drug response. Circulation 64:1089–1097, 1981