Nitroglycerin Infusion during Coronary-artery Surgery

Joel A. Kaplan, M.D.,* Ronald W. Dunbar, M.D.,† Ellis L. Jones, M.D.‡

The effects of an intravenous infusion of nitroglycerin were studied in 20 acutely hypertensive patients during coronary-artery surgery. Eight patients had histories of essential hypertension and six had been treated for it. They were anesthetized with morphine, diazepam, N₂O, O₂, pancuronium, and enflurane. Control measurements were obtained after sternotomy. Nitroglycerin was then administered until the blood pressure returned to normal, and the measurements were repeated. The mean dose of nitroglycerin was 50.0 ± 4.7 μg/min, or 0.96 μg/kg/min. This produced significant decreases (P < .05) in systolic, diastolic, and mean arterial blood pressures, central venous pressure, pulmonary capillary wedge pressure, systemic vascular resistance, and left ventricular stroke work index. Cardiac index, stroke index, and heart rate were unchanged. Two indices of myocardial oxygen demand (rate-pressure product and tension-time index) were significantly decreased by nitroglycerin (P < .005). Fifty per cent of the patients had improvement in ST-segment depression on the electrocardiogram. These findings demonstrate that nitroglycerin can be safely administered intravenously during operation, and suggest that nitroglycerin decreases myocardial oxygen demand and relieves myocardial ischemia. (Key words: Anesthetic techniques, hypotension, induced; Surgery, cardiac, nitroglycerin; Heart, coronary occlusion, nitroglycerin; Pharmacology, nitroglycerin.)

The frequency of coronary-artery operations has increased markedly in recent years. Direct bypass of the coronary arteries has been shown to relieve angina pectoris and, in some cases, to improve left ventricular function. One of the primary concerns of the anesthesiologist is to prevent intraoperative myocardial infarction. The currently reported incidences of this complication range from 5 to 40 per cent. In order to reduce this incidence, anesthesia and operation must interfere as little as possible with the delicate balance between myocardial oxygen demand and myocardial oxygen supply. Those factors that decrease the oxygen supply, such as hypoxia, hypotension, and arrhythmias, are well known. However, factors that increase oxygen demand have not been recognized as important until recently. Factors that increase myocardial oxygen demand include 1) increased intramyocardial wall tension secondary to either hypertension (increased afterload) or increased ventricular filling pressure (increased preload), 2) increased contractility, and 3) increased heart rate.

Intraoperative hypertension is a frequent problem in patients who have severe coronary-artery disease. Arens found significant hypertension in 36 per cent of his patients undergoing coronary-artery surgery. This elevation of the blood pressure leads to an increase in the myocardial oxygen demand, which is frequently associated with ischemic ST-segment changes on the electrocardiogram.

The remarkable efficacy of nitroglycerin in patients with ischemic heart disease has been recognized for years. Since nitroglycerin has been shown to affect the myocardial oxygen balance in patients with angina pectoris favorably by decreasing the myocardial oxygen demand, we decided to evaluate the possible beneficial effects of the intraoperative use of this drug during periods of increased oxygen demand associated with acute hypertension in patients undergoing coronary-artery operations.

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Methods and Materials

Twenty patients scheduled for elective coronary-artery operations were studied. They ranged in age from 41 to 60 years, and in weight from 60 to 106 kg (mean = 83.5 kg). All patients gave informed consent to the study, and the protocol was approved by the Emory University Clinical Trials Committee. All patients had good left ventricular function as defined by left ventricular end-diastolic pressure less than 12 mm Hg at the time of cardiac catheterization. Eight patients had histories of essential hypertension and six had taken antihypertensive medication. Only four patients were hypertensive prior to anesthetic induction. All medications were discontinued 48 hours prior to operation except propranolol, which was continued until 12-24 hours before operation, and sublingual nitroglycerin which was continued, as needed, until operation. All patients were premedicated with morphine (0.1 mg/kg), diazepam (0.1 mg/kg), and scopolamine (0.4 mg), intramuscularly, one hour before arriving in the operating room.

An 18-gauge Teflon catheter was inserted percutaneously into the right radial artery, and a 16-gauge catheter was inserted percutaneously into the superior vena cava via the right internal jugular vein for central venous pressure measurements. In six patients, a no. 7 Fr. triple-lumen Swan-Ganz catheter was placed in the pulmonary artery via the right internal jugular vein for measurement of pulmonary arterial pressure, pulmonary capillary wedge pressure, and central venous pressure. A 14-gauge peripheral venous catheter was inserted into each forearm for drug infusions. All pressures were monitored continuously with Hewlett-Packard 1250 transducers and recorded on a Siemens Mingograph 800 multichannel recorder.

In eight patients, an esophageal phonocardiogram was recorded from a microphone placed at the level of the right atrium. The phonocardiogram, along with the electrocardiogram and the arterial pulse wave, was used to measure systolic time intervals. The total electromechanical systole ($Q_S$), pre-ejection period (PEP), and left ventricular ejection time (LVET) were measured at a paper speed of 200 mm/sec. The ratios $PEP/LVET$ and $P/E$ were calculated from the measured variables.

Seven leads of the electrocardiogram were recorded for all patients. These included the three standard limb leads (I, II, III), three augmented limb leads (AVR, AVL, AVF), and a V$_3$ lead placed in the fifth interspace at the anterior axillary line. ST-segment depression was measured in the 7 leads using as electrocardiographic standardization (1 millivolt = 20 mm). The sum of the ST-segment depression was determined and this sum defined as $\Sigma ST$-segment.

Cardiac output was determined in duplicate by injection of 5 mg indocyanine green dye into the central venous pressure catheter and detection of the dye-dilution curve at the radial artery by a Gibson densitometer. The following variables were calculated using standard formulas: cardiac index, stroke index, left ventricular stroke work index, left ventricular minute work index, systemic vascular resistance, and pulmonary vascular resistance.

Two indirect indices of myocardial oxygen demand were calculated for all patients. The rate-pressure product (RPP) was calculated by multiplying heart rate by systolic blood pressure; the tension-time index (TTI) was calculated by multiplying heart rate by systolic blood pressure times left ventricular ejection time. The Buckberg index of endocardial viability was also calculated for the six patients with Swan-Ganz catheters using the following formula:

$$EVR = \frac{DPTI}{TTI} = \frac{(DP - PCWP)T_s}{MAP \times T_s}$$

where $EVR =$ endocardial viability ratio; $DPTI =$ diastolic pressure–time index; $TTI =$ tension–time index; $DP =$ diastolic pressure; $PCWP =$ pulmonary capillary wedge pressure; $MAP =$ mean arterial blood pressure; $T_s =$ systolic time; $T_n =$ diastolic time.

An aqueous solution of nitroglycerin was prepared by the Emory University Hospital pharmacy by the following method: 20 fresh nitroglycerin sublingual tablets (0.4 mg each) were dissolved in 20 ml physiologic saline.
solution under sterile conditions. The resulting solution, containing 8 mg nitroglycerin, was then passed through a Swinnex filter SXGS-025-05 and added to a 250-ml bag of 5 per cent dextrose in water. The final solution, consisting of 32 μg nitroglycerin per ml, was administered by a microdrop infusion set. A new solution was prepared every 8 hours. Multiple samples were subjected to sterility testing, and all were found to be sterile.

Patients were anesthetized with a standard technique consisting of morphine (0.5–1.0 mg/kg) and diazepam (0.3–0.5 mg/kg) for induction. Pancuronium bromide (0.1 mg/kg) was used to facilitate endotracheal intubation. Two minutes prior to tracheal intubation 3 ml of 4 per cent lidocaine was sprayed intratracheally. Anesthesia was maintained with 50 per cent nitrous oxide and oxygen in all patients. Seventeen patients also received 0.5–2 per cent inspired concentration of enflurane as required to deepen the anesthesia prior to the sternotomy. The inspired concentration of enflurane was kept constant in each patient during the study. Ventilation was controlled mechanically with a total gas flow of 5 l/min. Arterial oxygen tension (PaO₂) was maintained above 100 mm Hg and arterial carbon dioxide tension (Paco₂) between 35 and 40 mm Hg. No other drug was administered, and colloid was not infused during the period of the study.

All studies were performed after the sternum was opened and after 15 minutes of continuous stable hypertension. Measurements were made during a 45-minute period of stable anesthesia and surgical stimulation while the internal mammary artery was being dissected free from the chest wall. The indication for nitroglycer(6,4),(995,986)

### Table 1. Hemodynamic Values in 20 Patients

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<thead>
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<th>Control</th>
<th>Nitroglycerin</th>
<th>Significance</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SE</td>
<td>Mean</td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>169.7</td>
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<td>132.3</td>
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<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>93.9</td>
<td>2.4</td>
<td>77.3</td>
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<td>Mean blood pressure (mm Hg)</td>
<td>118.9</td>
<td>2.5</td>
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<td>Heart rate (beats/min)</td>
<td>81.0</td>
<td>2.2</td>
<td>83.9</td>
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<td>Central venous pressure (mm Hg)</td>
<td>12.9</td>
<td>0.8</td>
<td>10.1</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.9</td>
<td>0.2</td>
<td>2.8</td>
</tr>
<tr>
<td>Stroke index (ml/beat/m²)</td>
<td>35.9</td>
<td>3.4</td>
<td>34.9</td>
</tr>
<tr>
<td>Systemic vascular resistance (dynes/sec/cm²)</td>
<td>1722.4</td>
<td>155.0</td>
<td>1428.6</td>
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### Table 2. Additional Hemodynamic Data, Six Patients with Swan-Ganz Catheters

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<tr>
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<td>Mean</td>
<td>SE</td>
<td>Mean</td>
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<tr>
<td>Pulmonary capillary wedge pressure (mm Hg)</td>
<td>16.8</td>
<td>1.9</td>
<td>11.6</td>
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<tr>
<td>Mean pulmonary arterial pressure (mm Hg)</td>
<td>21.4</td>
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<td>Pulmonary vascular resistance (dynes/sec/cm²)</td>
<td>61.5</td>
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<tr>
<td>Left ventricular stroke work index (g·m/m²)</td>
<td>67.8</td>
<td>10.8</td>
<td>51.3</td>
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<tr>
<td>Left ventricular minute work index (kg·m/min/m²)</td>
<td>5.3</td>
<td>0.6</td>
<td>4.0</td>
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TABLE 3. Systolic Time Intervals, Eight Patients

<table>
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<th></th>
<th>Control</th>
<th>Nitroglycerin</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SE</td>
</tr>
<tr>
<td>Pre-ejection period (msec)</td>
<td>124.4</td>
<td>10.3</td>
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<tr>
<td>Left ventricular ejection time (msec)</td>
<td>467.0</td>
<td>10.1</td>
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<tr>
<td>Total electromechanical systole (QS) (msec)</td>
<td>591.4</td>
<td>15.8</td>
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<tr>
<td>PEP/LVET</td>
<td>0.29</td>
<td>0.03</td>
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<tr>
<td>L/PEP² (L/sec²)</td>
<td>72.1</td>
<td>13.2</td>
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data. A t value of less than 0.05 was considered significant.

Results

The mean dose of nitroglycerin needed to return the blood pressure to within 20 per cent of preoperative values was 50.0 ± 4.7 μg/min (0.95 ± 0.08 μg/kg/min). The range of doses was 32 to 128 μg/min (1-4 ml/min).

Hemodynamic values and derived indices for the 20 patients are presented in table 1. Additional hemodynamic data for the six patients with Swan-Ganz catheters are shown in table 2. With the nitroglycerin infusion, mean arterial blood pressure, central venous pressure, and pulmonary capillary wedge pressure decreased in each patient. Systolic, diastolic, and mean arterial pressures all decreased significantly (P < .005). Mean heart rate, cardiac index, and stroke index remained unchanged, while left ventricular stroke work and minute work indices decreased (P < .05). With a large decrease in pulmonary capillary wedge pressure, and a relatively smaller decrease in left ventricular stroke work index, the Starling point (position on the Frank-Starling myocardial function curve) moved down and to the left, indicating some improvement in left ventricular hemodynamics. Intravenous nitroglycerin also significantly decreased systemic vascular and pulmonary vascular resistances.

The results of systolic time interval measurements for the eight patients who had esophageal phonocardiograms are presented in table 3. The 15.2-msec increase in the pre-ejection period and the 38.7-msec decrease in left ventricular ejection time were both statistically significant. However, the total electromechanical systole did not change. Therefore, PEP/LVET increased and L/PEP² decreased.

Two indirect indices of myocardial oxygen demand were calculated (fig. 1). Both the rate-pressure product and the tension-time index were significantly decreased by nitroglycerin. In addition, the endocardial viability ratio increased from 0.90 ± 0.08 to 1.22 ± 0.11 in the six patients with Swan-Ganz catheters.

Since improvement in hemodynamics is not necessarily indicative of decreasing myocardial ischemia, we analyzed the ST segments of the electrocardiogram. Figure 2 shows the effect of nitroglycerin on the summation of ST-segment depression of the seven leads of the electrocardiogram for all 20 patients. In 50 per cent of the patients, nitroglycerin led to alleviation of ST-segment depression. This included all the acute ischemic ST-segment changes associated with hypertension. The remaining patients had slight nonspecific depressions of ST segments that did not change with nitroglycerin. None of the patients showed a further depression of the ST segment when blood pressure was lowered with nitroglycerin. The summation of the ST-segment depression decreased from 11.9 to 8.1 mm (P < .005). The majority of the improvement was in leads AVL and V₃. Figure 3 demonstrates a typical patient’s hemodynamic response to infusion of nitroglycerin. There is significant improvement in the ST segments in association with the hemodynamic changes. There was no perioperative myocardial infarction in these patients, and there was no hospital mortality.

Discussion

The use of vasodilators for improving left ventricular function and myocardial oxygena-
tion is currently gaining broad support. We chose to use and study nitroglycerin since it is the vasodilator that patients who have coronary-artery disease take preoperatively to relieve episodes of angina pectoris. Sublingual nitroglycerin has been shown to relieve angina largely through a reduction in myocardial oxygen demand. It has its primary effect on the venous capacitance bed, and results in peripheral pooling of blood and reduction of heart size and systolic wall tension. At larger doses, nitrates also appear to affect arteriolar tone. Sublingual nitroglycerin may also increase the supply of oxygen to the myocardium by causing redistribution of coronary blood flow to subendocardial ischemic areas.

Recent studies indicate that nitroglycerin may also be useful in management of patients who have acute myocardial infarction. It appears to improve ventricular function and to reduce the area of ischemic injury as measured by enzymatic and EKG changes. Other investigators report that sodium nitroprusside and phentolamine also improve left ventricular function in patients who have acute myocardial infarction, providing severe arterial hypotension is avoided.

We chose to administer the nitroglycerin by intravenous infusion to be able to titrate the dose precisely. Previously, Viljoen recommended intramuscular use of nitroglycerin during coronary-artery operations, and Lappas has used it sublingually. However, both of these methods may lead to unpredictable effects.

Fig. 1. Two indirect indices of myocardial oxygen demand are shown (mean ± SE). The rate pressure product (systolic BP × heart rate) is calculated for all 20 patients, and the tension time index (systolic BP × heart rate × left ventricular ejection time) for the seven patients in whom systolic time intervals were measured. The significant changes were mainly due to a decrease in the systolic blood pressure.

Fig. 2. Effect of 80.0 ± 4.7 μg/min nitroglycerin on the sum of ST-segment depression in all 20 patients (mean ± SE). AVL and V₅ most frequently detected the ST-segment changes.

Nitroglycerin has been administered intravenously in previous studies. Christensson administered doses ranging from 30 to 170 μg/min to normal volunteers in 1969, and, more recently, Flaherty and Stinson used infusions of nitroglycerin in patients with ischemic heart disease. All solutions were prepared in the same manner as ours and were sterilized by filtration. There has been no report of complications or toxicity.

There are a number of methods available to decrease myocardial oxygen demand intraoperatively. We elected to decrease preload and afterload rather than to depress myocardial contractility and cardiac output further with enflurane or propranolol. We selected nitroglycerin instead of nitroprusside for the following reasons: 1) preoperatively, the patients were taking nitroglycerin to decrease myocardial oxygen demand, and they knew their responses to the drug, valuable information for the anesthesiologist; 2) it is easy to control the dose and blood pressure response with minimal danger of producing hypotension; 3) nitroglycerin does not have any known toxicity; 4) most importantly, the effects of nitroglycerin on the coronary circulation have been extensively studied. Recently, Braunwald and Chiarlello presented evidence that nitroprusside may cause an intracoronary steal of blood from ischemic myocardium, while nitroglycerin does not have this effect. They postulated that this steal results from the primary arterial effect of nitroprusside, while the effect of nitroglycerin is mainly on the venous circulation. In their studies of patients and dogs with acute coronary insufficiency, nitroglycerin improved ST segments, while nitroprusside had a detrimental effect.

An increase in the heart rate is detrimental to patients who have ischemic heart disease because it increases myocardial oxygen demand while decreasing myocardial oxygen supply. Results of previous studies of the effect of nitroglycerin on heart rate have been conflicting. Some investigators report no change, while others have found small increases in heart rate (less than 15 percent). In our study, intravenous adminis-

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**Fig. 3.** A typical patient's electrocardiographic and hemodynamic responses to nitroglycerin. Improvement in lead V of the electrocardiogram is associated with hemodynamic changes indicating a decreased myocardial oxygen demand.
tation of nitroglycerin caused no significant change in heart rate. A number of factors may have prevented an increase in heart rate in our patients: 1) the presence of residual preoperative medications, including propranolol, digitalis, and reserpine; 2) anesthetic drugs, including morphine, diazepam, scopolamine, and enflurane; 3) impairment of autonomically mediated control of heart rate secondary to myocardial disease; 4) a gradual reduction of the blood pressure by nitroglycerin, characteristic in our experience.

The changes in systolic time intervals during nitroglycerin infusion were interesting. The pre-ejection period was prolonged by nitroglycerin, while the left ventricular ejection time was shortened, thereby producing an increase in the ratio PEP/LVET. Previously, Sawayama found similar changes in nitroglycerin in his noninvasive cardiac studies. This suggests that nitroglycerin decreased myocardial contractility, increased afterload, or decreased preload. Previous studies have shown that myocardial contractility does not change, or increases only slightly, with nitroglycerin; certainly the afterload does not increase with nitroglycerin. Therefore, the large decreases in central venous pressure and pulmonary-capillary wedge pressure (preload) provide the best explanation for the changes in the systolic time intervals. This also suggests that even the derived ratios l/PEP and PEP/LVET are affected by large changes in preload.

The electrocardiogram is our main monitor of myocardial ischemia in the operating room. Unfortunately, often only standard limb leads (I, II, III) are used. During the Master's stress test the anterior lateral chest wall leads provide the most useful information. We have found leads AVL and V₃ to be particularly useful in patients with left anterior descending coronary-artery disease. Five of the patients in this study had ST-segment changes evident only in these leads.

Nitroglycerin appears to be beneficial for patients who have acute intraoperative hypertension and myocardial ischemia during anesthesia and operation for coronary-artery insufficiency. Acute hypertension was relieved and myocardial oxygen demand was decreased in our cases as measured by rate-pressure product, tension–time index, and endocardial viability ratio. The earliest and most consistent effect of the nitroglycerin infusion was reduction in venous return to the heart (preload), as reflected in the pulmonary capillary wedge pressure and central venous pressure. By also reducing arterial pressure, the systolic wall tension generated in the left ventricle and the myocardial oxygen consumption were reduced. The beneficial effect of these changes was evident in the improvements in the ST segments of the electrocardiogram in 50 per cent of our cases.

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References