Comparison of Intravenous Nitroglycerin and Sodium Nitroprusside for Treatment of Acute Hypertension Developing after Coronary Artery Bypass Surgery


SUMMARY The present study was designed to test the hypothesis that i.v. nitroglycerin is as effective as sodium nitroprusside for managing acute hypertension early after coronary artery bypass surgery. Seventeen patients received both nitroglycerin and nitroprusside in a randomized crossover protocol. Infusion rates were increased stepwise to lower mean arterial pressures comparably with each drug. In 14 of 17 patients, similar infusion rates of the two vasodilators resulted in equal lowering of both blood pressure and systemic vascular resistance. In the remaining three patients, very high infusion rates of nitroglycerin were required and achieved only 20–50% of nitroprusside’s response in two of three. Hemodynamic responses to the two vasodilators were similar, except that nitroglycerin increased cardiac output more than nitroprusside did. In contrast, pulmonary gas exchange responses differed in that nitroglycerin improved intrapulmonary shunting, while nitroprusside worsened it. Similarly, nitroglycerin resulted in a significantly smaller increase in the alveolar-arterial oxygen gradient than did nitroprusside. These results suggest that in the majority of patients, i.v. nitroglycerin was as effective as nitroprusside in controlling acute hypertension after coronary artery bypass surgery. In addition, nitroglycerin appeared to have more favorable effects on pulmonary gas exchange. Because nitroglycerin has more beneficial effects on intercoronary collateral blood flow in the setting of regional ischemia, it may be preferable to nitroprusside in patients with ischemic heart disease.

Arterial Hypertension requiring i.v. vasodilator therapy occurred early after coronary artery bypass surgery in approximately two out of three patients in an earlier study from this institution. Although nitroglycerin is often viewed predominantly as a venodilator, our clinical studies of i.v. nitroglycerin in patients with acute myocardial infarction clearly indicate that, at higher infusion rates, nitroglycerin is also a potent arterial dilator. Nitroglycerin reduced both left ventricular filling pressure and mean arterial pressure, while stroke volume remained constant or increased. Lowering of peripheral vascular resistance was greatest in patients who had hemodynamic evidence of severe left ventricular failure.

In the present study, we used a randomized crossover protocol to determine whether i.v. nitroglycerin could be as effective as sodium nitroprusside in reducing arterial pressure in patients who were acutely hypertensive after coronary bypass. Previous studies have shown that nitroglycerin and nitroprusside can have opposite effects on the severity of regional ischemia. In these studies, nitroglycerin improved regional ischemia by increasing intercoronary collateral flow, while nitroprusside appeared to worsen ischemia by decreasing coronary perfusion pressure without improving collateral flow. Thus, if i.v. nitroglycerin is equally effective for treating acute hypertension in patients with coronary artery disease, it might be preferable to sodium nitroprusside.

Methods

The study population consisted of 17 patients undergoing coronary artery bypass surgery at The Johns Hopkins Hospital. Patients with a history of hypertension requiring drug therapy were excluded, but the study group was otherwise unselected. Written informed consent was obtained from all patients before surgery. Premedication included morphine and diazepam. Pancuronium bromide was used during intubation and the patients were mechanically ventilated throughout the study period. Anesthesia during the cardiac surgery was induced with i.v. diazepam, morphine, or thiamylol sodium. Anesthesia was subsequently maintained with i.v. morphine in 11 patients and fentanyl in six patients. Standard cardiopulmonary bypass with nonpulsatile flow rates of 2-2.5 l/min/m² was used. Systemic hypothermia (27–29º C), topical myocardial hypothermia and hyperkalemic cardioplegia were used. The aortic root was cross-clamped for periods of 10–60 minutes. All patients received heparin, 4 mg/kg; anticoagulation was reversed by protamine.

Before induction of anesthesia, a Swan-Ganz thermodilution catheter was placed in all patients to allow continuous monitoring of right atrial and pulmonary artery pressures. Cardiac output was serially measured by the thermodilution technique using 10-ml injections of 5% dextrose in water. Arterial pressure was monitored by a radial artery catheter and a Statham P23Db transducer. After surgery, all patients were transferred to the surgical intensive care unit and mechanical ventilation was continued. Significant postoperative hypertension was defined as the occurrence of a sudden and persistent (> 15 minutes) in-
crease in mean arterial pressure of at least 20 mm Hg (to mean arterial pressures of 95–150 mm Hg) during the first 3 hours after weaning from cardiopulmonary bypass. All patients were normotensive (mean arterial pressure 75–94 mm Hg) before the hypertensive episode. None were receiving vasopressor or vasodilator drugs before the study.

Hemodynamic variables at the time hypertension developed were recorded in all 17 patients before the initiation of vasodilator therapy. These variables included heart rate, cardiac output, mean arterial pressure, pulmonary capillary wedge pressure (or pulmonary artery diastolic pressure) and mean pulmonary artery pressure, as well as cardiac index, stroke work index, systemic vascular resistance index, pulmonary vascular resistance index and stroke volume index. After control measurements were obtained, patients were randomly assigned to one of two experimental protocols, depending on the last digit of their medical history number (fig. 1). Seven patients with even numbers received an infusion of sodium nitroprusside first and then crossed over to i.v. nitroglycerin. Ten patients with an odd number received i.v. nitroglycerin first and then crossed over to nitroprusside. The nitroglycerin solution, supplied by the Johns Hopkins Hospital Pharmacy, contained nitroglycerin, 250 μg/ml, in 50-ml glass ampules. Nitroprusside was prepared in a 500-μg/ml concentration and infusion lines from the syringe containing nitroprusside to the patient were covered with aluminum foil. The nitroglycerin solution was refrigerated in the dark during long-term storage, but did not require protection from light during short-term infusion.

Infusion of each drug was begun at 5–10 μg/min and increased stepwise every 3–5 minutes until mean arterial pressure was lowered 10–33% (10–40 mm Hg), depending on the starting value. Then, the hemodynamic effects were allowed to stabilize from approximately 20 minutes and cardiac output was remeasured to define a hemodynamic profile for the first vasodilator drug. The first vasodilator was then discontinued and infusion of the second drug begun. As the vasodilating effects of the initial agent began to decrease, the infusion rate of the second agent was increased in a stepwise fashion in an attempt to maintain mean arterial pressure at the same level reached with the first drug. When a stable infusion rate of the second vasodilator had been obtained, the hemodynamic effects were again allowed to stabilize for 20 minutes and cardiac output was remeasured to obtain a hemodynamic profile for the second vasodilator drug. Because all patients had significant drainage from their mediastinal tubes during the study, volume in the form of whole blood was administered simultaneously to replace surgical blood loss.

In eight of the 17 patients, pulmonary and tissue gas exchange were assessed by temporarily switching to an inspired oxygen concentration (FiO2) of 100% for 10 minutes during the control and each subsequent intervention period. Arterial oxygen tension (PaO2), mixed venous oxygen tension (PvO2), alveolar-arterial oxygen gradient (AaDo2), intrapulmonary shunting (Qs/Qt) and tissue oxygen use (MVO2) could thereby be measured or calculated during each of these periods.

All results are expressed as mean ± SD. Statistical analysis was by two-way analysis of variance–repeated measures test, and individual comparisons were made only when analysis of variance revealed significant (p < 0.05) differences.

Results

The mean infusion rate of sodium nitroprusside required in all 17 patients to obtain the desired lowering of mean arterial pressure was 95 ± 116 μg/min. The mean infusion rate of nitroglycerin required to obtain a comparable lowering of arterial pressure was 304 ± 440 μg/min. Fourteen patients responded to nitroglycerin infusions of less than 300 μg/min (range 8–292 μg/min). Of the remaining three patients, one required 1125 μg/min to obtain a comparable blood pressure lowering, the second received 1245 μg/min and yet obtained only 50% of the mean arterial pressure reduction obtained with nitroprusside (167 μg/min), and the third received 1245 μg/min and obtained only 20% of the reduction in blood pressure obtained with nitroprusside (250 μg/min). In the 14 patients who obtained comparable blood pressure lowering with infusion rates less than 300 μg/min, the mean infusion rate of nitroglycerin was 111 ± 116

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** The experimental protocol. All patients received both i.v. nitroglycerin and i.v. nitroprusside in a randomized crossover fashion. Arterial pressure (AP) and pulmonary artery pressure (PAP) were continuously monitored and cardiac output was measured by the thermodilution technique using Swan-Ganz balloon flotation catheters.
\( \mu g/min. \) This mean infusion rate of nitroglycerin was not significantly different from the average infusion rate of nitroprusside in these same patients.

After initiation of vasodilator therapy, arterial pressure decreased rapidly from a mean of 115 ± 18 mm Hg to 90 ± 9 mm Hg with nitroprusside and 90 ± 10 mm Hg with nitroglycerin (both \( p < 0.001 \) vs control) (fig. 2A). Systemic vascular resistance index decreased from an initially elevated level of 44 ± 9 units to normal levels of 31 ± 10 units with nitroglycerin and 31 ± 7 units with nitroprusside (both \( p < 0.001 \) vs control). Cardiac output increased from a control level of 2.4 ± 0.5 l/min/m² to 2.7 ± 0.7 l/min/m² with nitroprusside and to 2.9 ± 0.9 l/min/m² with i.v. nitroglycerin. Only the increase in cardiac output obtained with i.v. nitroglycerin was statistically significant (\( p < 0.025 \) vs control). The heart rate increased from 85 ± 14 beats/min during control to 93 ± 18 beats/min during nitroprusside and 93 ± 20 beats/min during nitroglycerin (both \( p < 0.025 \) vs control).

Because volume expanders were administered simultaneously with the vasodilator therapy, the preload-lowering effect of both agents was largely counteracted (fig. 2B). Left ventricular filling pressure (pulmonary capillary wedge pressure or pulmonary artery diastolic pressure), which was 11 ± 4 mm Hg before vasodilator therapy, was 10 ± 4 mm Hg during nitroprusside and 9 ± 3 mm Hg during i.v. nitroglycerin (NS). The control stroke work index was 38 ± 10 g-m/m² and did not change significantly with either drug (32 ± 7 g-m/m² during nitroprusside and 35 ± 12 g-m/m² during nitroglycerin). Stroke volume increased slightly with both vasodilators, from a control value of 54 ± 11 ml to 59 ± 19 ml during nitroglycerin and 56 ± 12 ml during nitroprusside (NS). The mean pulmonary artery pressure decreased from a control value of 17 ± 5 mm Hg to 15 ± 5 mm Hg with nitroglycerin and 16 ± 6 mm Hg with nitroprusside (NS) (fig. 2B). Control pulmonary vascular resistances were normal (< 4 units); consequently, small decreases in pulmonary vascular resistance index, from 2.8 ± 1.9 units to 2.2 ± 1.4 units during nitroglycerin and 2.4 ± 1.3 units during nitroprusside, were not expected to reach significance.

Nitroglycerin and nitroprusside had differential effects on pulmonary gas exchange (fig. 3). Mean \( Pao_2 \)
decreased from 397 ± 49 mm Hg during the control period to 363 ± 33 mm Hg during nitroprusside and 384 ± 27 mm Hg during nitroglycerin (NS). PVO₂ increased during nitroprusside and decreased during nitroglycerin. From a control level of 44 ± 10 mm Hg, PVO₂ decreased to 41 ± 6 mm Hg during nitroglycerin and increased to 46 ± 6 mm Hg during nitroprusside (NS). MVo₂ calculated by the Fick equation also increased with nitroglycerin and decreased with nitroprusside. Control MVo₂ was 101 ± 66 ml/min/m², compared with 111 ± 38 ml/min/m² during nitroglycerin and 84 ± 24 ml/min/m² during nitroprusside (NS).

AaDo₂ increased significantly with both vasodilators. However, the magnitude of the rise was greater with nitroprusside than with nitroglycerin (p < 0.025). AaDo₂ increased from a control level of 266 ± 26 mm Hg to 292 ± 27 mm Hg with nitroglycerin and to 331 ± 52 mm Hg with nitroprusside (both p < 0.025 vs control). Qs/Qt as calculated by the method of Berggren et al. also showed directionally opposite responses to I.V. nitroglycerin and nitroprusside. The shunt decreased from 22 ± 9% to 18 ± 2% with nitroglycerin and increased to 25 ± 5% with nitroprusside (p < 0.01).

The mean body temperature in all 17 patients during the control period was 35.7 ± 0.9°C. The mean body temperature was significantly higher during both nitroglycerin (36.2 ± 0.8°C) and nitroprusside infusion (36.0 ± 0.8°C) because the patients were gradually rewarming. However, because of the randomized crossover study design, mean temperatures were not different during nitroprusside and nitroglycerin periods.

The study patients had various hemodynamic profiles. Six patients had elevated filling pressures (13–18 mm Hg) and 11 patients had normal filling pressures (5–11 mm Hg). Three of the six patients with elevated left ventricular filling pressures had a depressed cardiac index (1.8–2.0 l/min/m²) and three had a normal cardiac index (≥ 2.5 l/min/m²). Ten of the 11 patients with normal filling pressures had a normal cardiac index.

In the six patients with elevated left ventricular filling pressures, pulmonary capillary wedge pressure decreased from 15 ± 2 mm Hg to 9 ± 2 mm Hg (p < 0.001) with nitroglycerin and to 13 ± 4 mm Hg with nitroprusside (p < 0.05). Patients with normal filling pressures showed no decrease in filling pressure with either vasodilator. Similarly, nitroglycerin reduced mean pulmonary artery pressure more than did nitroprusside in patients with initially elevated filling pressures. From a control of 22 ± 4 mm Hg, the mean pulmonary artery pressure decreased to 20 ± 6 mm Hg with nitroprusside (NS) and to 14 ± 5 mm Hg (p < 0.02 vs control) with nitroglycerin. There were no other significant differences in the hemodynamic effects of the two vasodilators in patients in either hemodynamic subgroup.

No complications occurred during the study. Mean arterial pressure remained greater than 80 mm Hg and reduction of the infusion rate after the desired blood pressure lowering had been obtained was not required. Mild sinus tachycardia (≤ 120 beats/min) occurred during nitroprusside infusion in four patients and during nitroglycerin infusion in four patients, without hemodynamic or electrocardiographic (standard 12-lead ECG) evidence of regional ischemia. Neither sinus bradycardia nor vomiting was encountered. Because the patients remained intubated and at least partially anesthetized throughout the study, subjective symptoms of headache or nausea could not be elicited.

Discussion

The present study demonstrates that I.V. nitroglycerin can, in the majority of cases, be as effective as sodium nitroprusside for the treatment of hypertension after coronary bypass surgery. Both vasodilators corrected the elevated systemic vascular resistance and the elevated mean arterial pressure.

Previous investigators have suggested that nitroglycerin was predominantly a venodilator, obtaining its beneficial effects in angina pectoris by increased venous pooling. In an initial study of I.V. nitroglycerin in patients with acute myocardial infarction, lower infusion rates (mean 37 µg/min) of nitroglycerin reduced left ventricular filling pressure while minimally lowering mean arterial pressure (mean decrease 7 mm Hg). This lowering of left ventricular filling pressure was most likely the result of a change
in the diastolic pressure-volume relationship of the left ventricle or an increase in contractility secondary to a reduction in ischemia. If peripheral venodilation alone were the mechanism, then venous return and thereby cardiac output should have decreased. In subsequent clinical studies, i.v. nitroglycerin at higher infusion rates (mean 57 μg/min) was a potent arterial dilator with a variable effect on stroke volume that depended on the presence or absence of left ventricular failure. Patients without left ventricular failure had a decrease in stroke volume as if they were moving leftward down the same Starling curve. This might be expected to result from venodilation and the associated reduction in venous return. Patients with mild-to-moderate left ventricular failure maintained or increased their stroke volume despite a significant reduction in their filling pressures, appearing to move leftward along the same flattened Starling curve or to shift upward and to the left to a more favorable Starling curve. Thus, patients with the greatest elevations of left ventricular filling pressure and the lowest stroke work obtained, in addition to the beneficial antiischemic effects demonstrated in all hemodynamic subgroups, the optimal hemodynamic effects as well.

We recently found that the incidence of acute hypertension during the first 5 hours after coronary artery bypass surgery was 61% (131 of 215 patients). We investigated the possible roles of renin-angiotensin and catecholamines in the pathogenesis of this syndrome. At peak hypertension, plasma catecholamine levels were highest and renin and angiotensin levels were low. Plasma catecholamine levels were comparably elevated in both hypertensive and nonhypertensive patients. The patients with postoperative hypertension were statistically more likely to have been receiving chronic propranolol therapy and at higher doses than patients without hypertension. The role of prior propranolol therapy in the pathogenesis of postoperative hypertension is uncertain.

By design, mean arterial pressure was lowered equally by the two drugs in the majority of patients; systemic vascular resistance was comparably lowered. At the time patients developed hypertension, systemic vascular resistance was markedly increased, associated with decreased cardiac output. One might have expected an increase in cardiac output and heart rate if excess β-adrenergic stimulation had been the cause. Instead, peripheral arterial constriction appeared to be the primary response with a secondary decrease in cardiac output. The mechanism responsible for this sudden increase in vascular resistance is unclear. Although we found that both renin and angiotensin were suppressed when hypertension developed, other investigators have reported elevated renin and angiotensin II levels. In our patients, renin and angiotensin levels appeared to decrease rapidly after the development of hypertension; slight differences in the timing of blood samples could explain this apparent contradiction. All patients were hypothermic (35–36°C) at the time of their hypertensive episode, but patients who developed hypertension were no more hypothermic than those who did not. Furthermore, the randomized sequence of administration of the two vasodilators should have neutralized differences directly related to this gradual postoperative rewarming.

Administration of nitroprusside to anesthetized patients has been shown to result in a decrease in Pao₂. In older patients and in patients with low preoperative Pao₂ values, Pao₂ decreased markedly, suggesting a worsening of ventilation-perfusion mismatch. Seltzer et al. found a similar decrease in Pao₂ in patients receiving nitroprusside for treatment of intraoperative hypertension. Several investigators have suggested that the mechanism by which nitroprusside worsens intrapulmonary shunting is inhibition of hypoxic vasoconstriction in the pulmonary vasculature, resulting in increased perfusion of poorly ventilated regions of the lung. Sublingual nitroglycerin caused only a small decrease in Pao₂ in a group of patients with chronic obstructive pulmonary disease (COPD). Similarly, in patients undergoing coronary artery bypass surgery, nitroglycerin may have more favorable effects on the alveolar-arterial oxygen gradient and, in turn, on intrapulmonary shunting than does nitroprusside. In addition, the increase in Pvo₂ with nitroprusside could be explained by inhibition of electron transport within mitochondria by cyanide, a metabolite of sodium nitroprusside.

Several investigators have compared the effects of nitroglycerin and nitroprusside on the severity of regional myocardial ischemia. Chiarello and coworkers administered both nitroglycerin and nitroprusside to patients with acute myocardial infarction and found directionally opposite effects on the severity of ischemia. The magnitude and extent of ST-segment elevation recorded by precordial ST-segment mapping worsened when they infused i.v. sodium nitroprusside. When they administered sublingual nitroglycerin to the same patients, ST-segment elevation was reduced. Chiarello et al. also performed a similar study in an animal model using radioactive microspheres to quantify regional myocardial blood flow. When they infused sodium nitroprusside, epicardial ST segments in the region of myocardium distal to the coronary ligation became more elevated and regional myocardial blood flow decreased. When they infused nitroglycerin and obtained comparable hemodynamic effects, ST-segment elevation in the ischemic region was reduced and myocardial blood flow in that region increased. Thus, nitroprusside appeared to worsen regional ischemia by reducing coronary perfusion pressure without augmenting collateral flow. In contrast, nitroglycerin appeared to improve ischemia by increasing flow through preexisting intercoronary collateral channels, out of proportion to its effect on perfusion pressure.

Subsequent studies have confirmed these differing effects of nitroglycerin and nitroprusside on regional myocardial blood flow. In dogs with well-developed collaterals induced by placement of an ameroid constrictor, Capurro et al. showed that i.v. nitroglycerin causes a greater reduction in intercoronary collateral resistance than does nitroprusside. In patients with coronary disease and angiographically demonstrable
collaterals, Mann et al.4 used the xenon washout technique to show that regional blood flow distal to a severe coronary stenosis increased after infusion of nitroglycerin but decreased after sodium nitroprusside. Using an animal model of regional ischemia induced by atrial pacing in the presence of a fixed coronary stenosis, we confirmed the ability of i.v. nitroglycerin to dilate intercoronary collateral channels.18 An increase in collateral blood flow became the dominant antiischemic effect when preload- and afterload-lowering effects of nitroglycerin were reversed by returning arterial pressure to control levels.

In conclusion, i.v. nitroglycerin and nitroprusside are effective for the management of acute hypertension after coronary artery surgery. Nitroglycerin and nitroprusside reduced arterial pressure and systemic vascular resistance equally in the majority of patients. Nitroglycerin appears to have more favorable effects on pulmonary gas exchange and intrapulmonary shunting, which may be important in managing postoperative patients with pulmonary hypertension or those with intrinsic lung disease and large intrapulmonary shunts. In view of the directionally opposite effects of nitroglycerin and nitroprusside on the severity of regional ischemia, nitroglycerin appears to be preferable for use in patients with ischemic heart disease.

References


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