Intravenous nitroglycerin administration during infrarenal aortic clamping

D.G. Bjoraker MD, P.R. Knight MD PH D

Twenty-five patients requiring infrarenal abdominal aortic clamping were studied during halothane, nitrous oxide anaesthesia. Aortic clamping caused reductions in cardiac index (CI), stroke volume index (SVI) and left ventricular stroke work index (LVSWI). Systemic vascular resistance (SVR) increased. In seven patients CI was less than $1.8 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$. Intravenous administration of nitroglycerin, $1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, for 20 minutes, accompanied by volume loading to maintain pulmonary capillary wedge pressure, resulted in a significant improvement in haemodynamic parameters. CI increased 24 per cent as a result of a 14 per cent increase in SVI and an eight per cent increase in heart rate. LVSWI increased 13 per cent and SVR decreased 21 per cent. The plasma nitroglycerin concentration at the time of these measurements was $2.9 \pm 1.0 \text{ ng} \cdot \text{ml}^{-1}$. Aortic unclamping resulted in a mean maximum decrease of $14 \pm 2 \text{ torr}$ mean arterial pressure. Epinephrine, norepinephrine and plasma renin activity gradually increased during the period of the anaesthetic.

Key words

ANAESTHETICS, VOLATILE, halothane; HORMONES, angiotensin II, plasma renin activity; NITROGLYCERIN; SYMPATHETIC NERVOUS SYSTEM, epinephrine, norepinephrine; SURGERY, vascular, infrarenal aortic clamping.

Patients requiring intraoperative infrarenal aortic clamping for surgical repair of the aorta usually have generalized vascular disease which may involve the coronary arteries. Abrupt increases in impedance to ventricular ejection resulting from aortic cross-clamping may precipitate myocardial ischaemia in these patients.^{1,2} However, left ventricular dysfunction can occur even without ischaemia being evident. In a dog model, nitroglycerin infusion improved ventricular function during the cross-clamp period, particularly in the heart depressed with barbiturate.³ Although sodium nitroprusside has been used advantageously during aortic clamping in man,^{2,4} the favourable redistribution of coronary blood flow into ischaemic areas attributed to nitroglycerin in both animals^{5,6} and man⁶ may make it more desirable than other vasodilators.

Vasodilators may also be useful in preventing or minimizing potentially severe aortic declamping hypotension. The sudden decrease in vascular resistance at the time of unclamping is the main cause of severe hypotension, which Vetto and Brant⁷ described as "declamping shock." Relative hypovolemia may exacerbate hypotension by limiting the increase in cardiac output necessary to compensate for the decreased resistance. Vasodilator treatment prior to or during aortic clamping with chlorpromazine, droperidol,^{8,9} phenoxybenzamine,¹⁰ aminophylline¹¹ or sodium nitroprusside^{2,4} have all been used to prevent severe rises in vascular resistance of the peripheral circulation still perfused after clamping. These agents permit prompt recognition of progressive hypovolemia by preventing inapparent compensatory rises in vascular resistance. Intravascular volume deficits may, therefore, be replaced before unclamping. Predictably, when filling pressures have been maintained, vasodilators have not aggravated unclamping hypo-

From the Department of Anesthesiology, University of Michigan Medical School, Ann Arbor.

Address correspondence to: David G. Bjoraker MD, Department of Anesthesiology, University Hospitals, 1405 E. Ann St., Ann Arbor, MI 48109, U.S.A.

TABLE I Medical profile of the patients studied

	<i>Abdominal aortic aneurysms</i>	<i>Peripheral vascular occlusive disease</i>
Total cases	15	10
Male	13	5
Female	2	5
Age (yr)	67 $\pm$ 2	61 $\pm$ 2
Prior myocardial infarction	11	5
Prior coronary artery bypass graft	1	2
Preoperative treatment of hypertension	9	8
History of smoking	13	9

Mean values $\pm$ SEM.

tension. Since nitroglycerin is a mixed vasodilator, reducing both preload and afterload, maintenance of filling pressures during its administration should also minimize unclamping hypotension.

This study reports the haemodynamic consequences of intravenous nitroglycerin administration after a control period of infrarenal aortic cross-clamping in patients anaesthetized with halothane and nitrous oxide. Catecholamine concentrations, plasma renin activity and nitroglycerin plasma concentrations were also measured.

Methods

Twenty-five consecutive patients, ten with peripheral vascular occlusive disease and 15 with an abdominal aortic aneurysm undergoing procedures requiring aortic clamping were studied. Informed consent was obtained from the patients and the protocol was in compliance with the University of Michigan Committee to Review Grants for Clinical Research and Investigation Involving Human Beings. Of the 25 patients studied 16 had had a myocardial infarction more than six months preoperatively demonstrated by electrocardiographic evidence or history (Table I). Three had undergone coronary artery bypass grafting and 17 had been treated with antihypertensive drugs. Four of the five patients receiving propranolol preoperatively were diagnosed as having essential hypertension. Propranolol and other antihypertensive drugs were administered the morning of surgery.

The patients were premedicated with morphine, 8–12 mg, and scopolamine, 0.4 mg, i.m. Prior to induction, a Swan-Ganz pulmonary artery catheter

with thermodilution cardiac output capability and a 20 s.w.g. radial artery catheter were placed after lidocaine infiltration. Electrocardiographic leads II and V₅ were monitored throughout the case. Following induction with thiethylal sodium, halothane by mask and pancuronium neuromuscular blockade, the trachea was intubated. One-half to one per cent halothane, 50 to 65 per cent nitrous oxide and intermittent pancuronium were used to maintain anaesthesia. With the aid of intermittent arterial blood gas analysis, the PaCO₂ was maintained between 4.6 kPa and 5.3 kPa. Blood oxygen saturation was greater than 96 per cent.

Data from the arterial catheter, pulmonary artery catheter and electrocardiogram were obtained by direct transfer of the appropriate signal to a Hewlett Packard 9845 computer for evaluation, display and storage. Cardiac outputs were measured by thermodilution in triplicate and entered into the data set manually. Full haemodynamic measurements were made: (1) prior to induction, (2) 15 minutes prior to aortic clamping, (3) 15 minutes after clamping, (4) 35 to 40 minutes after clamping following 20 minutes of intravenous nitroglycerin administration, and (5) after final clamp removal and propanamine sulfate administration. Constant inspired concentrations of halothane and nitrous oxide were maintained and additional pancuronium was not administered between the second and fourth measurement times.

The nitroglycerin infusion was prepared by the hospital pharmacy laboratory by dissolution of 20 mg of sublingual tablets (Nitrostat) in 250 ml of dextrose (5 gm·dl⁻¹) in water and passed through a

0.22 μm pore size filter. A syringe pump and polypropylene infusion circuit were used for the nitroglycerin administration. Comparison of the assayed concentration of nitroglycerin entering and exiting the infusion circuit verified the absence of adsorption. The intravenous nitroglycerin was infused at a rate of $1.0 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ after the third observation set had documented the effect of aortic clamping. Nitroglycerin plasma concentrations were assayed at measurement points three and four. Nitroglycerin assays were performed by a high performance liquid chromatographic analysis of the n-pentane extract of plasma by the Upjohn Center for Clinical Pharmacology at the University of Michigan.

During the administration of nitroglycerin, the pulmonary capillary wedge pressure was maintained at the level observed prior to nitroglycerin administration. Lactated Ringer's solution, stored blood or both were used for the volume loading. Quantitation of the additional fluid replacement required to maintain pulmonary capillary wedge pressure during nitroglycerin administration was abandoned since concurrent surgical blood loss prevented an accurate determination.

Three to five minutes prior to gradual clamp release nitroglycerin was stopped, the anaesthetic was decreased by discontinuing nitrous oxide and a continuous arterial pressure recording was made. Excessive increases in preload prior to the unclamping of the aorta were treated with additional increments of nitroglycerin. If the graft was bifurcated, a reduced dosage of nitroglycerin, 0.3 to $0.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, was restarted after unclamping of the first limb while the distal anastomosis of the second limb was completed. If the pulmonary artery pressure was excessive following restoration of blood flow and discontinuation of nitroglycerin, nitroglycerin was again administered and fluids were withheld. None of the 25 cases required more than 15 additional minutes of intravenous nitroglycerin. In all cases nitroglycerin had been discontinued before the last set of measurements.

Concurrent with each haemodynamic set, arterial samples were obtained for plasma epinephrine and norepinephrine concentrations and plasma renin activity. Blood samples were immediately iced and centrifuged, and the plasma was removed and frozen for later batch analysis. Epinephrine and norepinephrine were assayed by the radioenzymatic

assay method of Peuler and Johnson.¹² A commercially available kit (NEA-026, New England Nuclear, North Billerica, Massachusetts) was used for the radioimmunoassay of plasma renin activity. In a subset of nine patients angiotensin II concentrations were determined by radioimmunoassay.¹³ All samples for a substance from any one patient were analyzed in a single assay run.

All data were statistically analyzed using the Michigan Interactive Data Analysis System (MIDAS). Interval comparisons were performed using a paired *t* test with Dunnett's *t* statistic to correct for multiple *t* tests. Chi-square test or the Student's *t* test for unpaired data were used for comparisons between the two surgical groups. All data is expressed as mean $\pm$ standard error of the mean (SEM).

Results

Following the induction of anaesthesia and the start of surgery, a decrease in mean arterial pressure occurred ($p = 0.0014$), but was not accompanied by a significant change in the heart rate or wedge pressure ($p > 0.2$, Figure 1). The cardiac index decreased ($p = 0.0001$) secondary to a decrease in stroke volume ($p = 0.0008$). Systemic vascular resistance increased ($p = 0.046$) and left ventricular stroke work index decreased ($p < 0.0001$).

Initially the mean arterial pressure increased slightly (less than 15 torr) with aortic clamping, however, after 15 minutes of aortic clamping and blood loss, the mean arterial pressure had decreased from 96 ± 2 to 90 ± 3 torr ($p = 0.019$). Heart rate, pulmonary capillary wedge pressure and central venous pressure were not changed ($p > 0.7$). Additional decreases in cardiac index, 2.32 ± 0.12 to $2.00 \pm 0.10 \text{ l}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ ($p = 0.0004$), stroke volume index, 31.4 ± 1.6 to $27.0 \pm 1.4 \text{ ml}\cdot\text{m}^{-2}$ ($p = 0.0016$), and left ventricular stroke work index, 35.4 ± 1.6 to $28.5 \pm 1.5 \text{ g}\cdot\text{m}^{-1}$ ($p = 0.0003$) had occurred after 15 minutes of aortic cross-clamping. Systemic vascular resistance increased from 1787 ± 115 to $1929 \pm 135 \text{ dyne}\cdot\text{sec}\cdot\text{cm}^{-5}$ ($p = 0.025$). In seven patients, four with aneurysms and three with occlusive disease, cardiac index decreased below $1.8 \text{ l}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$.

During the 20 minutes of nitroglycerin infusion with the aorta clamped, sufficient volume was administered to keep the pulmonary capillary wedge pressure constant, 12.6 ± 0.8 torr compared

FIGURE 1 Hemodynamic changes are characterized by mean arterial pressure (MAP), heart rate (HR), pulmonary capillary wedge pressure (PCWP), systemic vascular resistance (SVR), cardiac index (CI), stroke volume index (SVI), and left ventricular stroke work index (LVSWI). Observations were made before induction of anaesthesia (AWAKE), during anaesthesia and surgery but prior to cross-clamping (PRECLAMP), 15 minutes after aortic cross-clamping (CLAMPED), after 20 minutes of nitroglycerin infusion (35 minutes following aortic cross-clamping) (NTG), and after full restoration of flow (FLOW RESTORED). Mean $\pm$ SEM and interval change significance are indicated.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

FIGURE 2 Norepinephrine, epinephrine, and plasma renin activity were measured during the surgical procedure coincident with each haemodynamic observation. Mean $\pm$ SEM and interval change significance are indicated. * $p < 0.05$, ** $p < 0.005$.

with 12.2 ± 0.8 torr prior to nitroglycerin administration ($p = 0.79$). Cardiac index increased from 2.00 ± 0.10 to 2.46 ± 0.11 $\text{l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ($p < 0.0001$), secondary to increases in stroke volume index from 27.0 ± 1.4 to 30.7 ± 1.4 $\text{ml} \cdot \text{m}^{-2}$ ($p = 0.0024$) and heart rate from 76 ± 3 to 81 ± 3 $\text{beats} \cdot \text{min}^{-1}$ ($p = 0.001$). Left ventricular stroke work index also increased from 28.5 ± 1.5 to 32.3 ± 1.8 $\text{g} \cdot \text{m}^{-1}$ ($p = 0.027$) following nitroglycerin administration. Systemic vascular resistance decreased from 1929 ± 135 to 1526 ± 75 $\text{dyne} \cdot \text{cm}^{-5}$ ($p = 0.0007$) with nitroglycerin. The rate pressure product increased as a result of an increased heart rate ($p = 0.018$). The change, however, was minimal, 9440 ± 390 compared to 10640 ± 520 $\text{torr} \cdot \text{beat} \cdot \text{min}^{-1}$. The mean plasma nitroglycerin concentration assayed at this time was 2.9 ± 1.0 $\text{ng} \cdot \text{ml}^{-1}$.

Plasma epinephrine, norepinephrine and renin increased progressively throughout anaesthesia and surgery (Figure 2), however, individual cases were quite variable. The increase in epinephrine following nitroglycerin administration was significant ($p = 0.0006$). Angiotensin II concentrations paralleled plasma renin activity ($r = 0.89$, $p < 0.0001$).

Thirteen of the 25 patients received treatment for hypertension in the first hour after anaesthesia. Ten of the 17 patients previously diagnosed as hypertensive required treatment. The decision to treat was made by an anaesthetist who was not involved in the

study, the recovery unit physician or the surgeon. The measured concentrations of renin and angiotensin II intraoperatively were significantly greater ($p = 0.0090$ and $p = 0.0066$, respectively) in those patients who required treatment of hypertension. However, intraoperative epinephrine and norepinephrine concentrations were significantly less raised in the treated patients ($p = 0.0033$ and $p = 0.0085$, respectively) than in the nonhypertensive patients.

Prior to unclamping of the aorta, the discontinuance of nitrous oxide and nitroglycerin resulted in a gradual blood pressure increase. A slight drop in blood pressure with unclamping occurred, followed by a complete return in less than five minutes. The mean maximum decrease associated with unclamping of the aorta was 14 ± 2 torr mean arterial pressure (Table II). The procedures carried out on these patients were of long duration and involved large fluid shifts. There was no significant difference between the surgical groups with the exception of a greater blood loss in the aneurysm group.

No electrocardiographic evidence of ischaemia was observed at any time in these patients. However, during the course of the study, three patients developed electrocardiographic evidence of ischaemia which required nitroglycerin therapy before aortic clamping. Subsequently, they were treated and excluded from the patients presented. In one study patient, postoperative creatine phosphokinase MB isoenzyme activities were indicative of myocardial infarction; however, neither other diagnostic studies nor the clinical course supported this diagnosis.

Discussion

The diminished cardiac index, stroke volume index and left ventricular stroke work index with a constant pulmonary capillary wedge pressure following aortic cross-clamping are good evidence of decreased left ventricular performance. Although an acute rise in arterial pressure was noted during the several minutes between occlusion and the measurement, this pressure increase was transient and a net decrease was documented 15 minutes after aortic clamping. The decreased reserve of the ventricles with coronary artery occlusion may be responsible for the decrease in mean arterial pressure observed. Attia *et al.*¹ found that an increase of seven torr in pulmonary capillary wedge pressure of five torr in central venous pressure with aortic

TABLE II Operative procedure data

	<i>Abdominal aortic aneurysms</i>	<i>Peripheral vascular occlusive disease</i>	<i>Combined</i>
Mean arterial pressure drop with declamping (torr)	14.8 $\pm$ 2.7	12.9 $\pm$ 3.3	14.1 $\pm$ 2.1
Blood loss (litre)*	3.7 $\pm$ 0.7	1.4 $\pm$ 0.2	2.8 $\pm$ 0.5
Blood transfused (litre)	2.9 $\pm$ 0.5	1.5 $\pm$ 0.2	2.3 $\pm$ 0.4
Crystalloid fluid administered (litre)	5.7 $\pm$ 0.5	5.4 $\pm$ 0.7	5.6 $\pm$ 0.4
Surgical time (h)	4.7 $\pm$ 0.3	5.3 $\pm$ 0.4	4.9 $\pm$ 0.2
Cases requiring treatment of postoperative hypertension	7	6	13

Mean values $\pm$ SEM.

* $p < 0.05$

clamping is associated with myocardial ischaemia. Concurrent blood loss during the first 15 minutes of aortic clamping may have obscured these changes since only one of the 25 patients demonstrated a significant (more than seven torr) increase in pulmonary capillary wedge pressure. No patient's central venous pressure increased more than five torr. Electrocardiographic evidence of ischaemia or ventricular irritability did not occur.

Improvement of cardiac performance, as demonstrated by increased cardiac index and left ventricular stroke work index in the presence of constant pulmonary capillary wedge pressure, was related to nitroglycerin administration. Although the filling pressure could have been safely increased, had decreased performance continued, this manoeuvre was not necessary. Our observations are in disagreement with Grindlinger *et al.*¹⁴ who reported less systemic blood flow during infusion of nitroglycerin and sodium nitroprusside following aortic cross-clamping. Presumably, this was related to their withholding of fluid and allowing pulmonary capillary wedge pressure to fall. In the patients reported in this study, volume loading to maintain preload allowed afterload reduction by this mixed vasodilator to be a major haemodynamic feature.

The use of nitroglycerin with volume loading is compatible with safe aortic unclamping; however, abrupt unclamping which would maximize hypotension was not performed. The administration of nitroglycerin prior to cross-clamping as well as throughout the entire period of aortic occlusion would be a logical extension of our observations, particularly when applied to the patient with known

myocardial ischaemia. Since routine administration to patients without ischaemic heart disease constitutes prophylactic therapy, justification requires comparison between treated and untreated groups. To establish the efficacy of such a regimen, a lower incidence of ischaemic and hypotensive episodes, improved myocardial performance and a lower incidence of renal insufficiency would be desirable. This study suggests that such a comparison may be valuable.

Catecholamine release does not appear to be greatly affected by clamping or the use of nitroglycerin, although the increase in epinephrine did achieve statistical significance following nitroglycerin infusion. The renin-angiotensin II axis previously has been shown to be activated during surgery of the abdominal aorta.^{15,16} The progressive rise observed throughout the procedure has been characteristic.

In conclusion, the administration of intravenous nitroglycerin at $1 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ during infrarenal aortic clamping did improve haemodynamic parameters. The use of nitroglycerin was associated with minimal unclamping haemodynamic changes and was not associated with major alterations in catecholamine concentrations or renin-angiotensin II axis activity.

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Résumé

Vingt-cinq patients à qui on devait imposer un clampage de l'aorte abdominale sous les artères rénales au cours de chirurgie, ont été étudiés pendant une anesthésie à l'halothane et au protoxyde d'azote. Le clampage aortique a causé des réductions de l'index cardiaque (CI), de l'index du volume d'éjection (SVI) et de l'index du travail d'éjection du ventricule gauche (LVSWI). La résistance vasculaire systémique (SVR) a augmenté. Chez sept patients, le CI était moins que 1.8 litres/min/m². L'administration intraveineuse de nitroglycérine 1 µg·min⁻¹·kg⁻¹ pendant 20 minutes associée à un remplissage vasculaire pour maintenir la pression capillaire pulmonaire bloquée a amélioré de façon significative le profil hémodynamique.

Le CI a augmenté de 24 pour cent à cause d'une augmentation de 14 pour cent du SVI et de huit pour cent de la fréquence cardiaque. Le LVSWI a augmenté de 13 pour cent et la SVR a diminué de 21 pour cent. La concentration de nitroglycérine plasmatique au moment des mesures était de $2.9 \pm 1 \text{ ng} \cdot \text{ml}^{-1}$. La levée de l'obstruction aortique a entraîné une diminution maximale moyenne de $14 \pm 2 \text{ ml}$ de mercure de la pression artérielle. L'épinéphrine, la norépinéphrine et l'activité de la rénine plasmatique ont graduellement augmenté pendant l'anesthésie.