

Plasma catecholamine changes during cardiopulmonary bypass: a randomised double blind comparison of trimetaphan camsylate and sodium nitroprusside

LAURA CORR, R M GROUNDS, M J BROWN, J G WHITWAM

From the Departments of Clinical Pharmacology and Anaesthesiology, Hammersmith Hospital and Royal Postgraduate Medical School, London

SUMMARY The effects of trimetaphan camsylate and sodium nitroprusside on the catecholamine response to cardiac surgery were compared in a randomised double blind study of twelve male patients undergoing elective myocardial revascularisation. The solutions were titrated to maintain a mean arterial pressure of 70-85 mm Hg before and after bypass and < 70 mm Hg during bypass. The rise in plasma adrenaline during cardiopulmonary bypass in the sodium nitroprusside group was significantly greater than that in the trimetaphan camsylate group. There was a smaller rise in plasma noradrenaline in the sodium nitroprusside patients but this was significantly higher than in the patients receiving trimetaphan camsylate.

Administration of trimetaphan camsylate provides a simple and effective way to reduce catecholamine release during cardiopulmonary bypass.

Cardiopulmonary bypass has been shown to be a potent stimulus to the release of catecholamines^{1 2} and may be associated with a high systemic vascular resistance.³ It is now standard practice to use vasodilators such as sodium nitroprusside⁴⁻⁶ or glyceryl trinitrate⁷ to ameliorate the haemodynamic consequences of cardiopulmonary bypass. Ganglion blocking agents prevent the release of catecholamines from sympathetic nerve terminals and the adrenal medulla. Previous work has shown that the use of a ganglion blocking agent to produce elective hypotension in hip replacement reduces the secretion of catecholamines associated with the surgical stimulation and with the reduction in arterial pressure.⁸

The aim of the present study was to compare the catecholamine response to cardiopulmonary bypass when trimetaphan camsylate (a short acting ganglion blocking agent) or sodium nitroprusside (a direct acting vasodilator) were used to control arterial pressure.

Requests for reprints to Dr Laura Corr, Department of Clinical Cardiology, Hammersmith Hospital, Du Cane Road, London W12 0HS.

Accepted for publication 25 February 1986

Patients and methods

PATIENTS

Twelve male patients (aged 36-64 years) undergoing elective coronary artery bypass grafting were studied. All had chronic stable angina and none had had a myocardial infarction within six months of the study. Eleven were taking a β_1 selective β blocking drug which was discontinued on the evening before operation. The patients were randomly allocated into two groups which proved to be well matched; Table 1 shows some demographic details of the patients studied. The protocol was approved by the ethics committee of the Hammersmith Hospital and Royal Postgraduate Medical School and the patients gave informed consent.

ANAESTHESIA

All patients received a standard premedication of papaveratum 20 mg, hyoscine 0.4 mg, and droperidol 5 mg intramuscularly one and a half hours before induction of anaesthesia. On arrival in the anaesthetic room a peripheral venous line and a radial artery cannula were introduced under local anaesthetic (plain lignocaine 1%). Anaesthesia was induced with a standard regimen of thiopentone

Table 1 Demographic details of patients

	Sodium nitroprusside Mean (range)	Trimetaphan camsylate Mean (range)
Age (years)	53.8 (46-58)	52.0 (36-64)
Weight (kg)	73.7 (57-90)	81.5 (68-95)
Height (metres)	1.73 (1.60-1.82)	1.74 (1.60-1.80)

4 mg/kg, pancuronium bromide 0.1 mg/kg, and fentanyl 10 µg/kg after which two internal jugular vein catheters were introduced. The patients were ventilated with intermittent positive pressure via an Engstrom ventilator with oxygen and nitrous oxide only. Body temperature was measured with a nasopharyngeal thermistor. Further fentanyl was administered as follows: before the skin incision (5 µg/kg); before sternotomy (5 µg/kg); at the start of cardiopulmonary bypass (5 µg/kg); and during rewarming immediately before coming off bypass (10 µg/kg). Thiopentone (3 mg/kg) was administered slowly for ten minutes immediately before bypass when the nitrous oxide was discontinued. Pancuronium (0.033 mg/kg) was administered at the start of bypass.

One of the two groups of patients received sodium nitroprusside (50 mg in 50 ml 5% dextrose) and the other trimetaphan camsylate (250 mg in 50 ml 5% dextrose). Previous preliminary work showed that these solutions cause similar falls in blood pressure when delivered at the same infusion rate. Coded solutions were presented foil wrapped and were given when required as an infusion via a Vickers Medical Treonic IP5 syringe pump. The rate of the infusion was titrated to maintain a mean arterial pressure of 70-85 mm Hg before and after bypass and not greater than 70 mm Hg during bypass.

OPERATION

Table 2 describes the main operative variables for each patient group. Cardiopulmonary bypass was instituted via a Harvey RA/IVC venous cannula and a Cimid No 28 aortic cannula and was maintained by a non-pulsatile roller pump (American Optical Roller Pumps) and a bubble oxygenator (Dideco Hi Flex 7000). Fluid from cardiotomy suction was filtered to 40 µm; no arterial line filter was used. Cardiac standstill was achieved by means of St

Table 2 Operative details of patients

	Sodium nitroprusside Mean (range)	Trimetaphan camsylate Mean (range)
No of grafts	3.33 (2-4)	3.16 (1-4)
Bypass time (min)	63.5 (43-88)	68.6 (30-106)
Cross clamp time (min)	35.5 (20-52)	35.3 (17-61)

Thomas' cardioplegia solution in Hartmann's solution. The roller pump was primed with 2000 ml Hartmann's solution and 25 ml 8.4% sodium bicarbonate. The pump flow rate was 2.4 l/min/m² at normal body temperatures and was reduced to 1.21 l/min/m² at 27°C. Rapid cooling to 27°C was induced; the average cooling time was 5 minutes in each group.

BLOOD SAMPLES

Blood was taken from the arterial circulation for measurement of plasma adrenaline and nor-adrenaline concentrations (a) after induction of anaesthesia (control value); (b) after median sternotomy (before cannulation of the great vessels); (c) 10 minutes after the start of cardiopulmonary bypass; (d) 30 minutes after the start of cardiopulmonary bypass; (e) 50 minutes after the start of cardiopulmonary bypass (in three patients bypass had been discontinued before this sampling point); (f) shortly after discontinuation of cardiopulmonary bypass when the patient was cardiovascularly stable; (g) at the insertion of the last sternal wire; and (h) at skin closure.

Samples were taken into lithium heparin bottles on ice, centrifuged at 4°C, and the plasma was stored at minus 70°C until assayed by a sensitive and specific double isotope radioenzymatic assay.⁹

STATISTICS

Results within each group were analysed by two way analysis of variance. Inter-group differences were assessed by analysis of covariance. Results are expressed as mean (SE).

Results

The mean volume of vasodilator solution required was 25.4 ml sodium nitroprusside (range 13-33 ml) and 21.6 ml trimetaphan camsylate (range 8-37 ml).

ADRENALINE (FIG. 1)

The plasma adrenaline concentration in the control samples was 0.014 (0.038) nmol/l in the sodium nitroprusside group and 0.098 (0.038) nmol/l in the trimetaphan camsylate group (normal range 0.055-0.819 nmol/l). There was no change in the trimetaphan camsylate group after sternotomy; in the sodium nitroprusside group there was a small rise to 1.31 (0.502) nmol/l ($p < 0.05$).

Plasma adrenaline increased considerably in the sodium nitroprusside group during bypass ($p < 0.001$) to a peak value of 5.775 (1.245) nmol/l after 30 minutes. Thereafter the plasma concentrations decreased but after 50 minutes on bypass they were still significantly higher than control val-

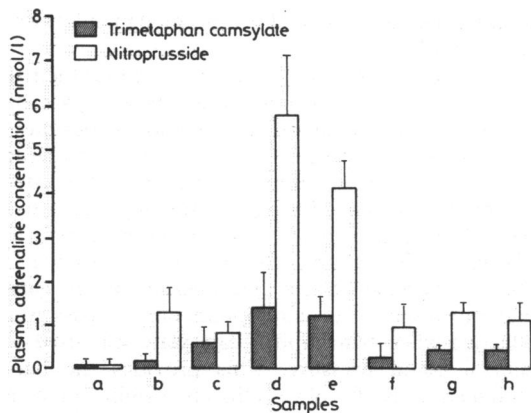


Fig. 1 Plasma adrenaline concentration during operation and cardiopulmonary bypass. Key to samples: (a) after induction of anaesthesia; (b) after median sternotomy; (c) after 10 min on bypass; (d) after 30 min on bypass; (e) after 50 min on bypass; (f) off bypass and in stable cardiovascular state; (g) after insertion of sternal wires; (h) at end of skin closure.

ues. Immediately after bypass the plasma adrenaline returned rapidly to concentrations not significantly different from those after median sternotomy (0.977 (0.459) nmol/l) and did not subsequently change.

In contrast there was only a small rise in the group given trimetaphan camsylate, reaching a peak value of 1.425 (0.742) nmol/l after 30 minutes on bypass. Overall there was a highly significant difference between the two groups ($p < 0.02$).

NORADRENALINE (FIG. 2)

Changes in plasma noradrenaline resembled those of adrenaline but were less pronounced. Again there was no difference between the two groups in the control period (2.849 (0.579) nmol/l and 2.86 (0.946) nmol/l in the sodium nitroprusside and trimetaphan camsylate groups respectively; normal range 1.182–4.728 nmol/l). There was a small but significant rise in the sodium nitroprusside group to 6.394 (1.874) nmol/l ($p < 0.05$) after median sternotomy. The sodium nitroprusside group, however, showed a highly significant rise in plasma noradrenaline to 17.334 (4.728) nmol/l during cardiopulmonary bypass ($p < 0.001$). Once off bypass the concentrations remained higher than during the control period. The trimetaphan camsylate group showed a smaller rise in noradrenaline (peak 7.6 (3.02) nmol/l) than the sodium nitroprusside group ($p < 0.05$). As with adrenaline, there was a significant difference between the two groups in the plasma concentrations during operation ($p < 0.05$).

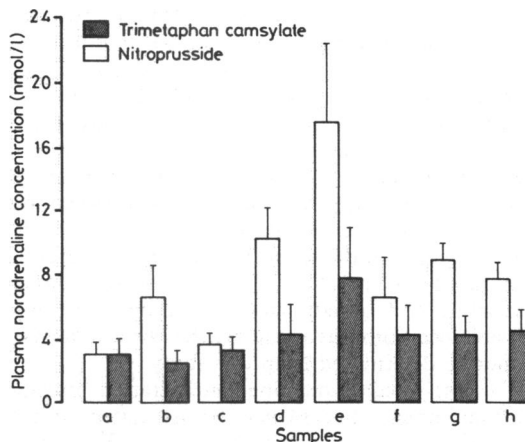


Fig. 2 Plasma noradrenaline concentration during operation and cardiopulmonary bypass. Key to samples: (a) after induction of anaesthesia; (b) after median sternotomy; (c) after 10 min on bypass; (d) after 30 min on bypass; (e) after 50 min on bypass; (f) off bypass and in stable cardiovascular state; (g) after insertion of sternal wires; (h) at end of skin closure.

TEMPERATURE AND pH

In both groups the temperature was rapidly reduced to 27°C during cardiopulmonary bypass. The lowest pH of 7.39 (corrected for temperature) was reached after 50 minutes on bypass. There were no significant differences in the temperature or pH between the two groups at any stage.

Discussion

This study demonstrates a striking rise in catecholamine concentrations during cardiopulmonary bypass when sodium nitroprusside is used to control blood pressure. This confirms the findings of other workers in animals^{10 11} and man^{12 13} since the advent of the radioenzymatic assay.⁹ Hitherto, analysis of catecholamines by fluorimetric methods led to diverse reports of changes during operation and cardiopulmonary bypass.^{14 15}

The increase in plasma adrenaline concentration was several times higher than the simultaneous increase in plasma noradrenaline. This resembles the response reported by Reves *et al.*^{12 16} Trimetaphan camsylate is administered intravenously and has a very short half life. Thus it is a suitable alternative to sodium nitroprusside during operation. Blood pressure was controlled rapidly and easily with trimetaphan camsylate and there were no side effects. The use of trimetaphan camsylate prevented the massive release of catecholamines found in the sodium nitroprusside group.

The cause of the rise in catecholamines remains unclear. Some workers have suggested that it is related to hypothermia or acidosis. Profound hypothermia may be associated with increases in catecholamines^{10 17} but there is no consensus on the effects of temperature on catecholamine release during cardiopulmonary bypass.¹⁸ In our study there was no difference in temperature or pH between the two groups and these factors cannot explain the lower response in the trimetaphan camsylate group. Ganglion blockade is likely to reduce the increases in adrenaline and noradrenaline in response to any physiological stimulus and hence the cause of the rise cannot be determined from this study.

The rise in catecholamine concentrations during cardiopulmonary bypass may be associated with a very high systemic vascular resistance.³ Engleman *et al* failed to show a significant correlation between the two,² but their study was complicated by the use of sodium nitroprusside which tends to have opposing effects on systemic vascular resistance and sympathetic drive. In our study the trimetaphan camsylate and sodium nitroprusside were titrated against mean arterial pressure. Since the flow rate of the pump was kept constant, the solutions were effectively titrated against the systemic vascular resistance and were administered only when this rose. The reduction of the catecholamine response when trimetaphan camsylate was used provides indirect evidence that the sympathetic drive is a major determinant of the high systemic vascular resistance during cardiopulmonary bypass. The high systemic vascular resistance may have adverse effects on tissue oxygen delivery and impair myocardial function immediately after bypass.^{19 20} Furthermore, perfusion of the heart on bypass via non-coronary collateral flow with blood containing high uncontrolled levels of catecholamines may further deplete the metabolic reserves of the arrested heart.²¹ Reperfusion of the ischaemic heart is a critical stage and the catecholamine concentrations at this time are extremely high.²²⁻²⁴ This has led some workers to speculate that β adrenoceptor antagonists or calcium channel blockers might be useful in protecting the heart from damage.¹² These agents have negative inotropic effects, however, and could cause important myocardial depression.

The potential advantage of ganglion blockade over adrenoceptor blockade is that all adrenergic responses are blocked irrespective of which adrenoceptor type is involved and which neurotransmitter is released; not only the cardiovascular system may be adversely affected by the sympathetic drive.²⁵ Concentrations of both the neuronally released noradrenaline and the circulating plasma adrenaline are sufficiently high to have pro-

found metabolic as well as haemodynamic consequences.²⁶⁻²⁸

Many attempts have been made to reduce the rise in catecholamines on cardiopulmonary bypass by means of different anaesthetic techniques, but these have proved unsuccessful.^{29 30} The use of pulsatile flow also failed to suppress the excessive catecholamine release during cardiopulmonary bypass,^{1 31} although in one study some reduction in plasma concentrations after bypass was shown.³² Our study demonstrates that blockade of the sympathetic response to cardiopulmonary bypass was effective when trimetaphan camsylate was used to control blood pressure. This provides the haemodynamic benefits of vasodilatation while reducing further harmful effects of the high sympathetic drive and circulating catecholamines.

References

- 1 Wallach R, Karp RB, Reves JG, Oparil S, Smith LR, James TN. Pathogenesis of paroxysmal hypertension developing during and after coronary bypass surgery: a study of haemodynamic and humoral factors. *Am J Cardiol* 1980; **46**: 559-65.
- 2 Engleman RM, Haag B, Lemeshow S, Angelo A, Rousou JH. Mechanism of plasma catecholamine increases during coronary artery bypass and valve procedures. *J Thorac Cardiovasc Surg* 1983; **86**: 608-15.
- 3 Hoar PF, Stone JG, Faltas AN, Bendixen HH, Head RJ, Berkowitz BA. Haemodynamic and adrenergic responses to anaesthesia and operation for myocardial revascularization. *J Thorac Cardiovasc Surg* 1980; **80**: 242-8.
- 4 Lappas DG, Lowenstein E, Waller J, *et al*. Haemodynamic effects of nitroprusside infusion during coronary artery operation in man. *Circulation* 1976; **54** (suppl 3): 4-10.
- 5 Palmer RF, Lasseter KC. Sodium nitroprusside. *N Engl J Med* 1975; **292**: 294-7.
- 6 Brown DR, Starek P. Sodium nitroprusside-induced improvement in cardiac function in association with left ventricular dilatation. *Anesthesiology* 1974; **41**: 521-3.
- 7 Kaplan JA, Dunbar RW, Jones KL. Nitroglycerine infusion during coronary artery surgery. *Anesthesiology* 1976; **45**: 14-21.
- 8 Hameji M, Tashiro C, Oka N, Seki T, Kawashima Y, Yoshiya I. Plasma catecholamine response to hypotension induced by trimetaphan and by sodium nitroprusside during nitrous oxide-oxygen-fentanyl anaesthesia. *Med J Osaka Univ* 1983; **34**: 37-41.
- 9 Brown MJ, Jenner DA. Novel double-isotope technique for enzymatic assay of catecholamines, permitting high precision, sensitivity and plasma sample capacity. *Clin Sci* 1981; **61**: 591-8.
- 10 Turley K, Roizen M, Vlahakes GJ, Graham B, Ebert PA. Catecholamine response to deep hypothermia and total circulatory arrest in the infant lamb. *Circulation* 1980; **62** (suppl I): 175-9.
- 11 Pitt BR, Gillis CN, Hammond GL. Depression of pul-

- monary metabolic function by cardiopulmonary bypass procedures increases levels of circulating norepinephrine. *Ann Thorac Surg* 1984; **38**: 508-13.
- 12 Reves JG, Karp RB, Buttner EE, *et al.* Neuronal and adrenomedullary catecholamine release in response to cardiopulmonary bypass in man. *Circulation* 1982; **66**: 49-55.
 - 13 Feddersen K, Aurell M, Delin K, Haggendal T, Aren C, Radegran K. Effects of cardiopulmonary bypass and prostacycline on plasma catecholamines, angiotensin II and arginine-vasopressin. *Acta Anaesthesiol Scand* 1985; **29**: 224-30.
 - 14 Hine IP, Wood WG, Mainwaring-Burton RW, Butler MJ, Irving MH, Booker B. The adrenergic response to surgery involving cardiopulmonary bypass, as measured by plasma and urinary catecholamine concentrations. *Br J Anaesth* 1976; **48**: 355-63.
 - 15 Tan C-K, Glisson SN, El-Etr AA, Ramakrishnaiah KB. Levels of circulating norepinephrine and epinephrine before, during and after cardiopulmonary bypass in man. *J Thorac Cardiovasc Surg* 1976; **71**: 928-31.
 - 16 Reves JG, Buttner E, Karp RB, Oparil S, McDaniel HG, Smith LR. Elevated catecholamines during cardiac surgery: consequences of reperfusion of the post-arrested heart. *Am J Cardiol* 1984; **53**: 722-8.
 - 17 Wood M, Shand DG, Wood AJJ. The sympathetic response to profound hypothermia and circulatory arrest in infants. *Can Anaesth Soc J* 1980; **27**: 125-31.
 - 18 Black PR, Van Devanter S, Cohn LH. Current research review: effect of hypothermia on systemic and organ system metabolism and function. *J Surg Res* 1976; **20**: 49-63.
 - 19 Kansal S, Roitman D, Kouchoukos N, *et al.* Ischaemic myocardial injury following aorto-coronary bypass surgery. *Chest* 1975; **67**: 20-7.
 - 20 Boudoulas H, Lewis RP, Vasko JS, *et al.* Left ventricular function and adrenergic hyperactivity before and after saphenous vein bypass. *Circulation* 1976; **53**: 802-6.
 - 21 Brazier J, Hottenrott C, Buckberg G. Noncoronary collateral myocardial blood flow. *Ann Thorac Surg* 1975; **19**: 426-35.
 - 22 Bretschneider HJ, Hubner G, Knoll D, Lohr B, Nordbeck H, Spieckermann PG. Myocardial resistance and tolerance to ischaemia: physiological and biochemical basis. *J Cardiovasc Surg (Torino)* 1975; **16**: 241-60.
 - 23 Kirklin JW, Conti VR, Blackstone EH. Prevention of myocardial damage during cardiac operations. *N Engl J Med* 1979; **301**: 135-41.
 - 24 Buckberg GD. A proposed "solution" to the cardioplegic controversy. *J Thorac Cardiovasc Surg* 1979; **77**: 803-15.
 - 25 Kopin IJ, Lake RC, Zeigler M. Plasma levels of norepinephrine. *Ann Intern Med* 1978; **88**: 671-80.
 - 26 Young JB, Landsberg L. Catecholamines and intermediary metabolism. *Clin Endocrinol Metab* 1977; **6**: 599-631.
 - 27 Young JB, Landsberg L. Catecholamines and the regulation of hormone secretion. *Clin Endocrinol Metab* 1977; **6**: 657-95.
 - 28 Brown MJ, Brown DC, Murphy MB. Hypokalaemia from beta₂-receptor stimulation by circulating epinephrine. *N Engl J Med* 1983; **309**: 1414-9.
 - 29 Stanley TH, Berman L, Green O, Robertson DH, Roizen M. Fentanyl-oxygen anaesthesia for coronary artery surgery: plasma catecholamine and cortisol responses [Abstract]. *Anesthesiology* 1979; **51**: S139.
 - 30 Stanley TH, Berman L, Green O, Robertson D. Plasma catecholamine and cortisol responses to fentanyl-oxygen anaesthesia for coronary artery operations. *Anesthesiology* 1980; **53**: 240-53.
 - 31 Landymore RW, Murphy DA, Kinley CE, *et al.* Does pulsatile flow influence the incidence of postoperative hypertension? *Ann Thorac Surg* 1979; **28**: 261-6.
 - 32 Philbin DM, Levine FH, Kono K, *et al.* Attenuation of the stress response to cardiopulmonary bypass by the addition of pulsatile flow. *Circulation* 1981; **64**: 808-12.