COMPARISON OF NITROPRUSSIDE AND NITROGLYCERINE FOR CONTROLLING HYPERTENSION DURING CORONARY ARTERY SURGERY

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SUMMARY

The haemodynamic effects of infusing sodium nitroprusside or trinitroglycerine to control hypertension during operation were compared in 22 patients undergoing coronary artery surgery. Measurements were taken before induction of anaesthesia, during median sternotomy, and upon attainment of a stable decrease in arterial pressure. Both drugs significantly decreased arterial pressure without affecting heart rate or cardiac output. Systemic vascular resistance, pulmonary capillary wedge pressure and left and right ventricular stroke work were decreased also. Although nitroglycerine significantly decreased pulmonary vascular resistance, and produced a significantly greater decrease in central venous pressure than nitroprusside, these differences are unlikely to be important clinically.

Systemic hypertension, sometimes accompanied by electrocardiographic evidence of ischaemia, is common before cardiopulmonary bypass in patients with coronary artery disease during revascularization operations, despite apparently adequate anaesthesia (Arens et al., 1972). Sympathetic nerve stimulation during median sternotomy may cause tachycardia and an increase in systemic vascular resistance, thus increasing ventricular stroke work and myocardial oxygen demands beyond available supply, and the patient is exposed to the danger of the perioperative infarct (Mundth and Austen, 1975).

Sodium nitroprusside (Lappas et al., 1976) and trinitroglycerine (Kaplan and Jones, 1979) have been advocated to control hypertension during cardiac surgery and this study was designed to compare these two drugs.

PATIENTS AND METHODS

Consecutive patients presenting for coronary artery bypass surgery were divided randomly into two equal groups to receive either sodium nitroprusside (SNP) or trinitroglycerine (TNG) during anaesthesia. Informed consent was obtained from each patient.

Patients

Eleven patients received SNP (nine male and two female) with a mean age of 53 yr (range 45–65 yr) and mean left ventricular end-diastolic pressure (LVEDP) on cardiac catheterization of 17 mm Hg (range 10–30 mm Hg). Eleven male patients received TNG (mean age was 51 yr, range 39–62 yr) with a mean LVEDP of 17 mm Hg (range 12–26 mm Hg). All patients had presented with angina and were treated with adrenergic beta-receptor blocking agents up to the evening before surgery. They were exercised before operation to the point of development of angina pectoris or S-T segment change on the electrocardiogram (e.g.), using a standard treadmill test, and rate-pressure products were calculated (Nelson et al., 1974).

Following premedication with lorazepam 2.5 mg orally (2 h before operation), and droperidol 5–10 mg plus fentanyl 50–100 μg i.m. (1 h before operation) each patient was brought to the operating theatre breathing oxygen. Cannulae were inserted, under local anaesthesia, to a peripheral vein and the radial artery. The e.c.g. (leads II and V5) was monitored and a triple-lumen thermodilution flotation catheter inserted into a branch of the pulmonary artery. The following baseline values were recorded before induction of anaesthesia: heart rate, systolic arterial pressure, mean arterial pressure, mean pulmonary artery pressure, mean pulmonary capillary wedge pressure, mean central venous pressure and cardiac output in duplicate by thermodilution (values accepted if within 5% of each other).

Anaesthesia, induced with droperidol 0.2 mg kg⁻¹ plus fentanyl 10 μg kg⁻¹ i.v. was maintained with a mixture of 50% oxygen and...
nitrous oxide delivered from a Blease ventilator. The trachea was intubated following the administration of pancuronium 0.1 mg kg⁻¹. Further increments of fentanyl and pancuronium were administered as necessary (judged clinically and by interpretation of a Cerebral Function Monitor recording). Ventilation was adjusted to produce $P_{a\text{CO}_2}$ between 4.5 and 5.5 kPa, as determined by repeated measurements of blood-gas tensions. Before median sternotomy a 14-gauge central venous catheter was inserted percutaneously into the left subclavian vein by the infraclavicular route to allow administration of SNP or TNG.

During surgical stimulation, the patients were allowed to exceed 75% of their calculated rate-pressure product and all variables measured again (control). Either fresh 0.01% sodium nitroprusside (Nipride, Roche) in 5% dextrose (protected from light) or 0.01% trinitroglycerine (Tridil, American Hospital Supply) in 5% dextrose was infused using an electronic finger-pump counter and micro-drip set, starting at 20 μg min⁻¹ and increasing by 20-μg increments each minute until mean arterial pressure decreased to between 70 and 80 mm Hg, and all measurements repeated (treatment). The time taken from commencement of infusion to attainment of a stable arterial pressure was noted. Blood losses were minimal during the study and were replaced on a 1:1 basis using 5% dextrose solution.

Additional variables were derived from the basic measurements as follows:

\[
\begin{align*}
CI &= \frac{CO}{BSA} \\
SI &= \frac{CI}{HR} \\
SVRI &= \frac{(AP - RAP)}{CI} \\
PVRI &= \frac{(PAP - PCWP)}{CI} \\
LVSWI &= \frac{1.36 \times (AP - PCWP)}{100} \times SI \\
RVSWI &= \frac{1.36 \times (PAP - RAP)}{100} \times SI \\
RPP &= HR \times SAP
\end{align*}
\]

where CI = cardiac index (litre min⁻¹ m⁻²); SI = stroke index (ml beat⁻¹ m⁻²); SVRI = systemic vascular resistance index (mm Hg litre⁻¹ min⁻¹); PVRI = pulmonary vascular resistance index (mm Hg litre⁻¹ min⁻¹); LVSWI = left ventricular stroke work index (g m m⁻²); RVSWI = right ventricular stroke work index (g m m⁻²); RPP = rate-pressure product (mm Hg beat min⁻¹); CO = cardiac output (litre min⁻¹); BSA = body surface area (m²); HR = heart rate (beat min⁻¹); AP = mean arterial pressure (mm Hg); RAP = mean right atrial pressure (mm Hg); PAP = mean pulmonary artery pressure (mm Hg); PCWP = mean pulmonary capillary wedge pressure (mm Hg) and SAP = systolic arterial pressure (mm Hg).

Results are expressed as mean ± standard error of the mean (SEM), and paired and unpaired Student t tests used for assessment of statistical significance.

**RESULTS**

The haemodynamic changes produced by SNP or TNG are presented in table I.

During opening of the chest and before preparation of the heart for cardiopulmonary bypass, surgical stimulation produced an increase in heart rate in both groups of patients (fig. 1). However, there was no further increase after the introduction of either SNP or TNG.

Median sternotomy was associated with marked systemic hypertension which was not ameliorated by increments of fentanyl 200 μg i.v. Within 1 min of commencing an infusion of SNP there was a decrease in mean arterial pressure and stability was achieved within 5 min at an average dose of 1.1 μg kg⁻¹ min⁻¹. There was a marked tendency to overshoot, but arterial pressures returned to baseline values within 4 min of stopping the infusion.

TNG produced a significant decrease in arterial pressure (fig. 2) which was more gradual in onset. The effects were seen within 2 min of commencing the infusion and stability was achieved within 7 min at an average dose of 2.8 μg kg⁻¹ min⁻¹. There was less tendency to overshoot than with SNP. Arterial pressures returned to their previous values within 5 min of withdrawing TNG.

The changes in mean arterial pressure were reflected in significant decreases in RPP (table II). Although two patients receiving SNP developed transient S-T segment depression during surgical stimulation, this reverted to normal during the infusion of SNP. S-T segments remained isoelectric throughout in the TNG group.

Left atrial pressures decreased markedly during administration of SNP or TNP and the latter agent
**Table I.** Hemodynamic effects of sodium nitroprusside (SNP) or trimetoglycerine (TNG) in patients during coronary artery surgery. Mean ± SEM. Symbols for statistical significance (Student's t tests): *P<0.05; **P<0.005. Difference in change of central venous pressure from control value produced by SNP compared with that produced by TNG was the only change statistically significant between SNP and TNG.

<table>
<thead>
<tr>
<th></th>
<th>SNP group (n=11)</th>
<th>TNG group (n=11)</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>SNP</td>
</tr>
<tr>
<td>Heart rate (beat min⁻¹)</td>
<td>88±6</td>
<td>89±5</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>120±7</td>
<td>75±2**</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mm Hg)</td>
<td>20±2</td>
<td>12±2**</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mm Hg)</td>
<td>15±2</td>
<td>6±1**</td>
</tr>
<tr>
<td>Central venous pressure (mm Hg)</td>
<td>4±1</td>
<td>3±1*</td>
</tr>
<tr>
<td>Cardiac index (litre min⁻¹ m⁻²)</td>
<td>2.05±0.15</td>
<td>2.04±0.15</td>
</tr>
<tr>
<td>Stroke index (ml beat⁻¹ m⁻²)</td>
<td>23.8±1.9</td>
<td>23.4±1.8</td>
</tr>
<tr>
<td>Systemic vascular resistance index (mm Hg litre⁻¹ min m²)</td>
<td>60±5.7</td>
<td>37.3±3**</td>
</tr>
<tr>
<td>Pulmonary vascular resistance index (mm Hg litre⁻¹ min m²)</td>
<td>2.69±0.48</td>
<td>2.56±0.39</td>
</tr>
<tr>
<td>Left ventricular stroke work index (g m⁻²)</td>
<td>32.9±2.7</td>
<td>21.5±1.6**</td>
</tr>
<tr>
<td>Right ventricular stroke work index (g m⁻²)</td>
<td>4.8±0.61</td>
<td>2.76±0.31**</td>
</tr>
<tr>
<td>Rate-pressure product (mm Hg beat min⁻¹)</td>
<td>14571±1669</td>
<td>9114±742**</td>
</tr>
</tbody>
</table>

**Fig. 1.** Changes in heart rate from pre-induction values (pre-op), during surgical stimulation (control), and after vasodilator therapy (treatment). Values are expressed as mean ± SEM. Changes from control for both drugs were not significant; differences between drugs not significant. — = Nitroglycerine group, - - - = nitroprusside group.

Produced a slightly greater decrease in right atrial pressure than that achieved by SNP.

Cardiac index and stroke index decreased in both groups after the induction of anaesthesia (fig. 3) despite an increase in mean arterial pressure with surgical stimulation. These indices were unaffected by the infusion of SNP or TNG.

Systemic vascular resistance index decreased markedly in both groups during treatment.

Although the decrease was greater in the patients receiving SNP the difference was not statistically significant. Pulmonary vascular resistance was unaffected by SNP but decreased significantly with TNG although the difference between the groups was not significant.

Left ventricular performance was improved markedly by both drugs (figs. 4, 5). Two patients in the SNP group and five in the TNG group who
TABLE II. Rate-pressure product (mm Hg beat min⁻¹). Differences between SNP and TNG not significant

<table>
<thead>
<tr>
<th></th>
<th>Sodium nitroprusside</th>
<th>Trinitroglycerine</th>
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</thead>
<tbody>
<tr>
<td>Angina threshold on exercise treadmill</td>
<td>17755</td>
<td>16053</td>
</tr>
<tr>
<td>Maximum RPP during sternotomy</td>
<td>14571 ± 1669</td>
<td>12521 ± 956</td>
</tr>
<tr>
<td>RPP after stability achieved with vasodilators</td>
<td>9114 ± 742</td>
<td>9318 ± 686</td>
</tr>
</tbody>
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FIG. 3. Effects of nitroprusside (---) or nitroglycerine (----) on cardiac index (CI). Changes within groups and difference between groups not significant.

possessed normal left atrial pressures and stroke work indices during surgical stimulation responding normally to vasodilatation by concomitant decreases in both parameters. Nine patients treated with SNP, and six patients treated with TNG, who had abnormally high left atrial pressures during surgical stimulation, responded to vasodilatation by a decrease in left atrial pressure to normal without any corresponding decrease in ventricular stroke work.

DISCUSSION

Sympathetic nerve stimulation increases myocardial oxygen consumption by increasing heart rate, augmenting contractility, and increasing intramyocardial wall tension secondary to increased afterload (hypertension) or increased preload (increased ventricular filling pressures) (Braunwald, 1971).

Measurement of the rate-pressure product as a guide to myocardial oxygen consumption ($V_mO_2$) during anaesthesia is controversial and has its advocates (Dunbar, 1979) and detractors (Kissin and Mardis, 1980). Since the components of the RPP produce opposite effects on myocardial oxygenation, changes in RPP may not accurately reflect changes in $V_mO_2$ (Barash and Kopriva, 1980). An increase in heart rate increases $V_mO_2$ and decreases the time available for coronary filling during diastole. An increase in systolic arterial pressure may increase $V_mO_2$ but may also improve myocardial oxygenation by increasing coronary perfusion pressure. Thus, a patient with tachycardia and hypotension may be in greater danger of suffering ischaemic cardiac damage than one with a numerically similar RPP produced by systolic hypertension and a normal heart rate. In this study, increases in heart rate and systolic arterial pressure were evenly matched in both groups, hence RPP measurement could be expected to provide a reasonable clinical guide to an increase in $V_mO_2$ and the possibility of ischaemia, whilst accepting the limitations of this index as outlined above.

One approach to the control of hypertension and tachycardia during anaesthesia for coronary artery
surgery is to utilize maximal beta-blockade by continuing treatment right up to the morning of surgery. However, such therapy may impair the normal inotropic response of the heart to the moderate haemodilution which occurs after cardiopulmonary bypass, and so produce a situation where the cardiac output cannot increase sufficiently to guarantee adequate oxygen transport to the tissues (Clarke et al., 1980). An alternative is to increase the depth of anaesthesia by the administration of inhalation agents. However, halothane, enflurane and trichloroethylene cause depression of ventricular function, especially in the presence of beta-adrenergic blocking agents (Stephen, Davie and Scott, 1971; Foëx et al., 1974 Horan et al., 1977), and are associated with high ventricular filling pressures and poor endocardial viability ratios (Maunuksela, 1977; van Ackern et al., 1979).

Investigations in dogs using epicardial mapping (Bland and Lowenstein, 1976), and direct measurement (Smith, Rogers and Thorburn, 1980) have demonstrated that halothane improves the ratio of oxygen supply to demand in experimentally-produced myocardial ischaemia in the presence of normal ventricular filling pressures. This beneficial effect has yet to be demonstrated in the presence of increased ventricular filling pressures in man. It would therefore seem logical to control hypertension during operation by the adoption of an anaesthetic technique which has a reputation for maintaining cardiovascular stability without depressing ventricular function (Tyden and Westerholm, 1979) by using moderate beta-blockade (by discontinuing beta-blocking agents 12–24 h before surgery) and augmenting these with direct-acting vasodilators.

Kaplan and Jones (1979) compared nitroprusside with nitroglycerine freshly prepared in the hospital pharmacy and showed that both drugs directly affect vascular smooth muscle and will decrease arterial pressure by a balanced dilation of resistance and capacitance vessels during anaesthesia. They found that coronary perfusion pressure was better maintained by TNG, a conclusion supported by other workers (Chiariello et al., 1976).

In this study, both drugs controlled the intraoperative hypertension by decreasing mean arterial pressure adequately without affecting heart rate or cardiac output, showing that myocardial contractility was unaffected by either agent. The decreases in arterial pressure with both agents were accomplished by decreases in systemic vascular resistance and hence left ventricular afterload. In addition, TNG significantly decreased pulmonary vascular resistance. Left and right ventricular filling pressures were decreased significantly by both drugs. TNG produced a greater reduction in right atrial pressure than SNP which, although statistically significant, was not large enough to be of clinical significance. The decrease in preload reduced left ventricular end-diastolic pressure and decreased ventricular wall tension without substantial alterations in stroke work, suggesting that myocardial oxygen consumption was reduced without impairing cardiac output.

During anaesthesia, no patient exceeded that rate-pressure product which was associated with angina or S-T changes when exercised before operation (table II) and this may explain why only two patients, both in the SNP group, showed S-T depression which disappeared shortly after commencing SNP infusion. Interestingly, these chan-
uges were only apparent in the lateral chest lead (V5), demonstrating the importance of monitoring this lead during operation for the detection of ischaemic episodes of the left ventricle (Kaplan and King, 1976).

Nitroglycerine was administered via a plastic giving-set incorporating a burette, and it has been shown that, when used in this way, much of the drug diffuses into the plastic (Cossum et al., 1978). This may explain why doses of TNG required to achieve haemodynamic stability were consistently greater than those reported elsewhere. Absorption may be minimized by infusing TNG using glass syringes coupled with high-density polyethylene connecting tubing. As an alternative the manufacturer could increase the concentration of the agent in the ampoule.

The conclusions to be drawn from this study are that both drugs improve ventricular performance whilst reducing myocardial oxygen consumption, and that there appear to be no clinically important haemodynamic differences between their effects. The change in central venous pressure produced by TNG was significantly greater than that produced by SNP, but the magnitude of the decrease in absolute terms is unlikely to be clinically significant. This opinion is supported by the fact that similar reductions in pulmonary capillary wedge pressure occurred with each agent. Although this study has failed to demonstrate any marked haemodynamic differences between the two drugs, nitroglycerine may be preferred for its more controllable decrease in arterial pressure coupled with less tendency to overshoot.

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COMPARAISON DU NITROPRUSSIATE ET DE LA
NITROGLYCERINE POUR CONTROLLER
L'HYPERTENSION PENDANT UNE INTERVEN-
TION CHIRURGICALE A L'ARTERE CORONAIRE

RESUME
On a compare sur 22 patients subissant une intervention
chirurgicale a l'artere coronaire, les effets hémodynamiques
d'une injection de nitroprussiate de sodium a ceux de la
trinitroglycérine pour contrôler l'hypertension pendant
l'opération. On a pris les mesures nécessaires avant l'induction
de l'anesthésie, pendant la sternotomie mediane et au moment
où l'on a atteint une diminution stable de la pression artérielle.
Ces deux agents ont fait baisser d'une manière significative la
pression artérielle sans affecter la fréquence ou le débit
cardiaque. La résistance vasculaire systémique, la pression
capillaire pulmonaire en coin et le travail systolique
ventriculaire gauche et droit ont également diminué. Bien que
la nitroglycérine ait fait baisser significativement la résistance
vasculaire pulmonaire, et qu'elle ait plus fortement réduit la
pression veineuse centrale, ces différences ne semblent pas
avoir une importance clinique.

VERGLEICH ZWISCHEN NITROPRUSSID UND
NITROGLYZERIN ZUR KONTROLLE VON
HYPERTENSION BEI
KORONARARTERIENOPERATIONEN

ZUSAMMENFASSUNG
Die hämodynamischen Effekte einer Injektion von
Natriumnitroprussid oder von Trinitroglyzerin zur Kontrolle
von Hypertension während der Operation wurden an 22
Patienten während Koronararterienoperationen verglichen.
Messungen wurden vorgenommen vor Einleitung der Narkose,
während der Mediansternotomie und nach Erzielung einer
stabilen Senkung des arteriellen Druckes. Beide Drogen
senkten den arteriellen Druck deutlich, ohne Herzrhythmus
oder Herzminutenvolumen zu beeinflussen. Der systemische
Gefäßwiderstand, der Lungenkapillardruck und der linke
und rechte Ventrikelsschlag wurden ebenfalls gesenkt. Obwohl
Nitroglyzerin den Lungengefäßwiderstand deutlich senkte,
und auch eine wesentlich stärkere Senkung des zentralvenösen
Druckes bewirkte als Nitroprussid, sind diese Unterschiede
klinisch wahrscheinlich kaum von Bedeutung.

COMPARACION DEL NITROPRUSIATO Y DE LA
NITROGLICERINA PARA EL CONTROL DE LA
HIPERTENSION DURANTE LA OPERACION DE LA
ARTERIA CORONARIA

SUMARIO
Los efectos hemodinámicos de la infusión de nitroprusiato de
sodio o de trinitroglicerina para controlar la hipertensión
durante la operación, se comparó en 22 pacientes sometidos a
operación de la arteria coronaria. Se efectuaron medicaciones
antes de administrar la anestesia, durante la esternotomía
mediana y al logro de una disminución estable de la presión
arterial. Ambas drogas disminuyeron significativamente la
presión arterial sin que el ritmo cardíaco ni la producción
cardíaca quedaran afectados. También se disminuyeron la
resistencia sistémico vascular, la presión gradual de los
capilares pulmonares y el trabajo de bombeo ventricular
izquierdo y derecho. Aunque la nitroglicerina disminuyó
significativamente la resistencia vascular de los pulmones y
produjo una mayor y más significativa disminución en la
presión venosa central que el nitroprusiato, no es probable
que estas diferencias sean de importancia clínica.