Pharmacological vasodilatation improves efficiency of rewarming from hypothermic cardiopulmonary bypass

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Summary
An afterdrop in core temperature after hypothermic cardiopulmonary bypass (CPB) is related to inadequate peripheral rewarming. We proposed that pharmacological vasodilatation during rewarming on bypass would improve peripheral rewarming and reduce the degree of afterdrop. Fifty-nine of 120 patients were randomized to receive a sodium nitroprusside (SNP) infusion during the rewarming phase of hypothermic CPB. Mean systemic vascular resistance (SVR) during the rewarming phase of CPB was 1129 dyne s⁻¹ cm⁻⁵ in the control group and 768 dyne s⁻¹ m⁻⁵ in the SNP group (P = 0.001). Patients receiving SNP rewarmed to 37.0 °C faster (299 min vs 376 min; P = 0.003) and were extubated earlier (490 min vs 621 min; P = 0.001). Patients receiving SNP had a warmer mean peripheral temperature (MPT) (32.9 °C vs 32.4 °C; P = 0.05) on termination of CPB. Postoperative core temperature fell less in the SNP group (35.6 °C vs 35.2 °C; P = 0.01) as did MPT (31.8 °C vs 31.2 °C; P = 0.004). SNP-induced vasodilatation during rewarming from hypothermic CPB improves peripheral rewarming, reduces the degree of postoperative core and peripheral hypothermia and reduces time to extubation. (Br. J. Anaesth. 1998; 81: 147–151)

Keywords: surgery, cardiopulmonary bypass; hypothermia; sodium nitroprusside

During hypothermic cardiopulmonary bypass (CPB), core temperature is usually reduced to below 30 °C to reduce tissue oxygen consumption and afford some degree of cerebral and myocardial protection. Despite apparently adequate rewarming as judged by a normal core temperature on termination of CPB, moderate postoperative hypothermia is common. Morbidity from postoperative hypothermia includes increased time to extubation, increased myocardial work and oxygen consumption, impaired coagulation, increased risk of wound infection and prolonged hospital stay. Postoperative hypothermia cannot be explained by heat loss to the environment alone and is thought to result from a failure of heat transfer to vasoconstricted peripheral tissues during rewarming on CPB, with a subsequent shift of heat from a warm core to a cold periphery. Increasing blood flow to vascular beds by increasing pump flow during rewarming on bypass reduces the degree of postoperative hypothermia, but the resultant pressure in the arterial cannula of the extracorporeal circuit may cause mechanical damage to blood. Pharmacologically-induced vasodilatation has been proposed as a method to limit postoperative hypothermia by improving rewarming of constricted vascular beds. In this previous study, pharmacological vasodilatation was combined with increased pump flow, and therefore increased heat delivery to the patient, so that the contribution of each factor to the subsequent reduction in postoperative hypothermia was unclear. This study was designed to determine whether pharmacological vasodilatation alone during the rewarming phase of hypothermic CPB would improve the efficiency of rewarming and reduce postoperative hypothermia.

Patients and methods
After obtaining local Ethics Committee approval, 120 sequential patients undergoing elective first-time coronary artery bypass grafting or valve replacement, or both, were entered into the study after written informed consent. Patients with peripheral vascular disease, diabetes mellitus or those subsequently returning to theatre for operation were excluded. Using a binary random number generator, patients were randomly assigned to a control group or to receive sodium nitroprusside (SNP). SNP was administered via a syringe driver (Graseby 3400) from the start of rewarming on CPB to the termination of CPB at a rate adjusted manually to give a mean arterial pressure (MAP) of 40 mm Hg. MAP during rewarming in the control group was not adjusted other than to maintain MAP below 80 mm Hg using 1-mg increments of phenolamine as is our usual practice. Patients receiving SNP did not receive inotropic or vasoconstrictor agents concurrently. Peri-operative management was otherwise identical in both groups.

Patients received lorazepam 2 mg orally 2 h before operation followed by morphine 5–10 mg i.m. and scopolamine 0.2–0.4 mg i.m. 1 h before surgery. Radial artery and peripheral venous cannulas were inserted under local anaesthesia. Anaesthesia was induced using midazolam 0.02–0.05 mg kg⁻¹ i.v., fentanyl 10–15 μg kg⁻¹ i.v. and pancuronium 0.1 mg kg⁻¹ i.v. The trachea was intubated and the lungs mechanically ventilated using oxygen in nitrous oxide, adjusted to maintain normocapnia. A heat and moisture exchanger was placed in the breathing circuit. A
central venous catheter was then inserted. Anaesthesia was maintained using propofol 80–150 mg h\(^{-1}\) and isoflurane to 1.2% as necessary. Midazolam 4 mg and pancuronium 4 mg were added to the pump prime fluid.

Core temperature was measured using a calibrated tympanic membrane thermocouple temperature probe (Mallinckrodt, Northampton, UK) placed before induction of anaesthesia after visually confirming with an otoscope that the external auditory meatus was free from wax. Peripheral temperature was recorded using four calibrated thermistors (Yellow Springs 400) placed on the chest wall, upper arm, thigh and calf before induction of anaesthesia. Mean skin temperature (MST) was calculated using a weighted equation as described by Ramanathan:

\[
\text{MST} = 0.3 \text{ (chest wall+upper arm)+0.2 (leg+thigh)}
\]

All temperatures were recorded to a temperature logger at 1-min intervals from induction of anaesthesia until postoperative core temperature had returned to 37.0°C.

The CPB unit incorporated a Dideco D703 (Sorin, Italy) hollow fibre membrane oxygenator with integral heat exchanger primed with lactated Ringer’s solution. During hypothermic CPB, core temperatures were reduced to 28–30°C. Pump flow during cooling and rewarming was adjusted according to a standardized local procedure. Flow was indexed at 2.4 litre min\(^{-1}\) m\(^{-2}\) above 30°C, 1.8 litre min\(^{-1}\) m\(^{-2}\) between 28–30°C, and 1.2 litre min\(^{-1}\) m\(^{-2}\) below 28°C, except during cooling when it was reduced to approximately 1.2 litre min\(^{-1}\) m\(^{-2}\). Rewarming aimed to restore the patients core temperature to 37°C before termination of CPB.

Heat extracted and returned to patients whilst on CPB was recorded using a previously described energy balance machine. The apparatus comprised an IBM compatible personal computer running dedicated software which interactively collects data from a specifically designed energy flux measurement system. The calculation of energy balance is based upon the Pick principle using pump flow and arterial and venous temperature in the perfusion circuit.

Net thermal energy balance (TEB) is calculated from the equation:

\[
E = sp \int_0^t (T_a - T_v) Q(t) \, dt
\]

where: \(E\) = net thermal energy balance during CPB (kJ), \(Q\) = pump flow at time \(t\) (litre min\(^{-1}\)), \(s\) = specific heat capacity of blood (3.84 kJ kg\(^{-1}\)C\(^{-1}\)), \(p\) = density of perfusate (approximately 1.0 kg litre\(^{-1}\)), \(a\) = arterial infusion temperature (°C), \(v\) = venous infusion temperature (°C), \(t\) = time.

The temperatures of arterial and venous blood were recorded at the inflow and outflow to the heat exchanger/oxygenator unit using previously calibrated thermistor probes (Electromedics Inc, Englewood CO 80112 USA, model No 4700 M344700) specifically adapted to fit the gold insulated temperature probe ports on the inflow to the heat exchanger (Tv) and the outflow from the oxygenator (Ta). Rotation of the pump was detected by an infrared reflective sensor placed over the pump head cover. As a marked limb passed beneath the detector, the sensor registered one rotation equivalent to 46-ml volume. The energy flux measured each minute was summated to give an instantaneous TEB. TEB is thus zero at commencement of bypass, becomes negative as the patient is cooled, and returns to a positive value as the patient is rewarmed before termination of bypass.

Operating theatre and intensive care environments were maintained at a stable state as allowed by the air conditioning. Operating theatre temperature was maintained between 20–24°C and relative humidity between 38–50%. Temperature in the intensive care unit was maintained between 22–25°C. No heating/cooling mattress was used during the operation. After bypass, all i.v. crystalloid, colloid and blood products were administered through a blood warmer heated to 37.8°C until core temperature reached 37°C. Patients were covered by a standard hospital woolen blanket and cotton sheet. No active postoperative warming was used.

Adequacy of rewarming was assessed by recording the coldest postoperative core temperature, following termination of CPB (fig. 1a) and the time for the postoperative core temperature to return to 37°C following afterdrop (fig. 1b). Time rewarming on bypass was the time from the start of rewarming to the termination of CPB (fig. 1c). Time to extubation was the time from the end of bypass to extubation of the patient. The doctor deciding when to extubate the patient was blinded to the group to which the patient was allocated. Statistical analysis was performed with Microsoft Excel 5.0 using unpaired two-way \(t\) tests. Results are given as mean values with confidence intervals (CI) for the mean difference between the control and SNP group. Significance was taken as \(P<0.05\).

**Results**

One hundred and twenty patients were studied, of whom 59 were randomly assigned to receive SNP. There was no significant difference between control

![Figure 1](image-url)  
**Figure 1** Core temperature changes during hypothermic cardiopulmonary bypass. 1 = Induction; 2 = start of active cooling on cardiopulmonary bypass; 3 = stop active cooling; 4 = start rewarming; 5 = separation from cardiopulmonary bypass. A = Coldest post-operative core temperature following termination of CPB; B = time for the post-operative core temperature to return to 37.0°C following the afterdrop; C = time rewarming on bypass.
and SNP groups in patient characteristics or environmental conditions. Patient characteristics are given in table 1. Ventilation was controlled manually for two patients in the control group for a prolonged period because of cardiovascular instability in one patient and postoperative bleeding in the other. Time to extubation of these patients was therefore excluded from the data. The power of the study was calculated from the time to rewarm to 37 °C in both groups. Standardized difference was 0.564 giving a power of 0.87 using the nomogram described by Altman. Mean arterial pressure during the rewarming phase of CPB was 53.5 mm Hg in the control group and 40.1 mm Hg in the SNP group (95%CI 10.8 to 15.9 mm Hg; P≤0.001). This equates to a mean systemic vascular resistance (SVR) of 1129 dyne s⁻¹ cm⁻⁵ and 768 dyne s⁻¹ cm⁻⁵ respectively. There was no significant difference in the amount of perioperative i.v. fluid administered to the two groups.

Time to rewarm to 37 °C was 376 min in the control group compared with 299 min in the SNP group (95%CI 28 to 129 min; P=0.003). Time to extubation was 621 min in the control group compared with 490 min in the SNP group (95%CI 70 to 232 min; P=0.001).

Patients receiving SNP had a warmer MST on termination of bypass (32.9 °C) compared with the control group (32.4 °C) (95%CI 0.06 to 0.94 °C; P=0.05). There was no difference in core temperature on termination of bypass between the control group (38 °C) and SNP group (38.1 °C) (95%CI -0.41 to 0.18 °C; P=0.52).

Postoperative core temperature decreased further in the control group (35.2 °C) than the SNP group (35.6 °C) (95%CI 0.1 to 0.6 °C; P=0.01). Minimum postoperative peripheral temperature was warmer in the group receiving SNP (31.8 °C) compared with control (31.2 °C) (95%CI 0.14 to 0.90 °C; P=0.004). Once postoperative core temperature had returned to 37.0 °C, there was no difference in the core-peripheral temperature difference between the control (3.65 °C) and SNP groups (3.59 °C) (95%CI -0.3 to 0.5; P=0.72).

There was no difference in time spent rewarming on bypass between control group (30.6 min) or SNP group (31.8 min) (95%CI -2.8 to 5.2 min; P=0.55). Bypass pump flows during rewarming were 8.4% higher in the SNP group (control 3.92 compared with SNP 4.25 litre min⁻¹; 95%CI 0.17 to 0.48 litre min⁻¹; P<0.001). Although there was no difference in mean thermal energy balance between control (805 kJ) and SNP groups (764 kJ) (95%CI -59.9 kJ to 141.7 kJ; P=0.42), a power of 0.05 was insufficient to conclude that this was a true negative result.

Discussion

Our results showed that pharmacological vasodilation with SNP during the rewarming phase of CPB warmed the patient more efficiently as shown by warmer peripheral temperatures on termination of bypass, suggesting that heat transfer to peripheral vascular beds had been increased through increased blood flow. The subsequent postoperative hypothermia was less in patients receiving SNP, shown by greater postoperative minimum core and peripheral temperatures and shorter time to rewarm to 37 °C. Clinically, improved rewarming resulted in earlier extubation.

Postoperative hypothermia is commonly seen in patients after hypothermic CPB and is greater than that observed in patients undergoing thoracic operations not requiring the use of CPB. Hypothermia during CPB causes intense vasoconstriction and greatly reduces blood flow through peripheral vascular beds such as muscle and fat. During the rewarming phase of CPB, the periphery is slow to warm because of the reduced blood supply to these vascular beds and the periphery remains relatively hypothermic when CPB is discontinued, despite attainment of a normal core temperature. Once bypass is discontinued, the core temperature decreases as heat is transferred to the cold periphery. Evidence for this theory is growing. Pharmacological vasodilation may force the periphery to vasodilate during rewarming, increase blood flow and heat transfer to the cold peripheral tissues, thereby reducing the subsequent decrease in core temperature.

The use of vasodilation during rewarming from hypothermia on CPB was first reported by Noback and Tinker. Twenty control patients were compared with eight patients receiving SNP during rewarming on bypass. SNP was administered at a rate to maintain MAP ≥70 mm Hg as CPB pump flows were increased. Increased CPB pump flow alone during rewarming increases perfusion of muscle beds and reduces the degree of postoperative hypothermia. Thus, although the study of Noback and Tinker reduced the degree of postoperative hypothermia, the relative contribution of increased heat delivery

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics and environmental conditions.</th>
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<tr>
<td></td>
<td>Control group</td>
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<tr>
<td>Theatre temp. (°C)</td>
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<td>ITU temp. (°C)</td>
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<td>Body surface area (m²)</td>
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<td>Mean SNP dose (µg kg⁻¹ min⁻¹)</td>
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<td>Rate of post-op. propofol infusion (ml h⁻¹)</td>
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<tr>
<td>Cardioplegia volume (ml)</td>
<td>1227</td>
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and pharmacological vasodilatation is difficult to distinguish.

Aps, Hutter and Williams\textsuperscript{14} reviewed the postoperative progress of 143 cardiac surgery patients in whom specific attempts to ensure adequate rewarming on bypass had been made. Patients received infusions of either SNP or glyceryl trinitrate (GTN) at a maximum rate that still allowed for adequate arterial perfusion pressures during rewarming on bypass (details not given). Rewarming was further optimized by the use of patient insulation, use of a warming mattress and heating of inspiratory gases to 40 °C. Although this technique minimized the degree of postoperative hypothermia, the relative contributions of each technique cannot be distinguished.

Both GTN and SNP have been used as peripheral vasodilators in these earlier studies. Recent work suggests that both GTN and SNP have similar arteriovenous vasodilatory profiles.\textsuperscript{15} SNP however was chosen in preference to GTN for this study because its greater potency and shorter half-life make it more suitable for acute haemodynamic manipulation. SNP dilates large arteries,\textsuperscript{16} small arteries and arterioles,\textsuperscript{15} suitable for acute haemodynamic manipulation. SNP is not known to possess any thermogenic properties.\textsuperscript{17} SNP however was not used as peripheral vasodilators in these earlier studies. Recent work suggests that SNP is not known to possess any thermogenic properties.

By using the same rewarming plan for control and SNP groups, we hoped to achieve the same bypass flow rates during rewarming in both groups. Surprisingly, flow was 8.4% higher ($P < 0.001$) in the SNP group. Although it may be expected that increased flow would be associated with increased heat delivery (TEB) during rewarming to the SNP group, the power of 0.05 for these data is insufficient to distinguish any difference between the two groups. Although the relative contribution of increased CPB flow and vasodilatation to heat transfer cannot be distinguished directly, the small difference in CPB flow between our two groups and the differential changes in core–peripheral temperature in the SNP group leads us to believe that SNP was at least partially responsible for the observed differences.

In addition, the core temperature at the end of bypass was the same in both groups. We therefore believe that the observed differences between the control and SNP groups are attributable, at least in part, to the effects of pharmacological vasodilatation. The larger differences in peripheral temperature between the control and SNP groups observed by Noback and Tinker\textsuperscript{6} may be caused by higher flows enabling a higher rate of SNP infusion and a greater degree of peripheral vasodilatation.

We avoided the use of warming blankets during rewarming from bypass and forced warm air convection blankets postoperatively because vasodilatation combined with active surface warming increases heat transfer to the patient\textsuperscript{19} and may mask the effects of thermal energy redistribution in the body caused by the SNP infusion. Noback and Tinker used heating mattresses during the rewarming phase of CPB in 16 of the 20 patients in the control group and 6 of the 8 patients in the SNP group.\textsuperscript{6} They failed to show any difference between the two groups but this may be because of the small numbers in the study.

Operating room and intensive care unit temperature varied by up to 4.0 °C. Other studies investigating postoperative rewarming have been unable to control ambient temperature more closely than our study\textsuperscript{6} or do not report environmental conditions.\textsuperscript{20–22} Environmental temperature did not show any significant correlation with time to rewarm to 37 °C or coldest postoperative temperature.

By increasing peripheral blood flow, SNP administered during rewarming on bypass appears to improve the efficiency of peripheral rewarming and reduce the degree of postoperative hypothermia.

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References


