The management of temperature during hypothermic cardiopulmonary bypass: II – Effect of prolonged hypothermia

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In animals mild hypothermia (32–35°C) reduces ischaemic brain injury, but this has not been investigated in humans. During hypothermic cardiopulmonary bypass (CPB) patients are made hypothermic (usually to 30–32°C) but are then rewarmed at a time when they are still at risk of ischaemic brain injury. We investigated the feasibility and safety of maintaining mild hypothermia throughout the CPB period. Thirty adult cardiac surgical patients were randomized to either rewarming to 36–37°C or to maintaining temperature at 34°C without rewarming. On arrival in the recovery room, patients in the hypothermic group had a mean bladder temperature of $33.8 \pm 0.45^\circ\text{C}$ compared with $35.4 \pm 0.58^\circ\text{C}$ (mean $\pm$ SD, $P < 0.05$) in the rewarmed patients. There were no differences between groups in intra- or postoperative blood loss or blood use, inotrope use, dysrhythmias, or myocardial infarction. The hypothermic group received more muscle relaxant for the treatment of shivering postoperatively. Our results suggest that mild hypothermia following CPB did not increase morbidity although larger studies are needed for confirmation.

Chez l'animal, l'hypothermie légère atténue le dommage cérébral causé par l'ischémie, ce qui n'a jamais été vérifié chez l'humain. Sous circulation extracorporelle (CEC) hypothermique, la température corporelle est abaissée (ordinairement à 30–32°C) mais les patients sont réchauffés alors qu'ils sont toujours à risque de dommage cérébral ischémique. Nous avons étudié la faisabilité et la sécurité offertes par l'hypothermie légère pendant la CEC. En chirurgie cardiaque, trente adultes sont répartis au hasard soit pour le réchauffement à 36–37°C soit pour le maintien de la température à 34°C sans réchauffement. À l'admission à la salle de réveil, les patients du groupe hypothermique présentent une température vésicale moyenne de $33,8 \pm 0,45^\circ\text{C}$ comparativement à $35,4 \pm 0,58^\circ\text{C}$ (moyenne $\pm$ ET, $P < 0,05$) pour les patients réchauffés. On ne trouve pas de différence entre les groupes pour ce qui est des pertes sanguines per- et postopératoires, l'utilisation des inotropes, les troubles du rythme et l'infarctus du myocarde. Le groupe hypothermique reçoit plus de curarisants pour le traitement des frissons postopératoires. Nos résultats suggèrent que l'hypothermie légère après CEC n'augmente pas la morbidité bien que des études plus vastes soient nécessaires pour le confirmer.

Key words

TEMPERATURE: hypothermia, hypothermic;
SURGERY: cardiac, cardiopulmonary bypass;
COMPLICATIONS: neurological.

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During hypothermic CPB patients are made hypothermic but then rewarmed at a time when they are at risk of ischaemic brain damage due to micro- or macroemboli, as well as hypotension, haemodilution, and other factors associated with CPB.^{1,2} Studies in experimental animals demonstrate that mild brain cooling (2–5°C) confers dramatic protection from ischaemic brain injury.³ Hypothermia may, however, be associated with adverse effects such as excessive bleeding, cardiac arrhythmias, depressed drug metabolism, as well as imbalance of oxygen supply and demand (whole body and myocardial) during shivering.⁴ The present study was designed to investigate the feasibility and safety of using extended mild hypothermia as a strategy to provide neuroprotection to patients undergoing hypothermic CPB.

Methods

With approval from the Human Research Ethics Committee and after obtaining informed consent 30 patients undergoing elective, first, cardiac surgery requiring CPB were randomly assigned to either standard or experimental temperature management. For the standard group the perfusionist was instructed to cool the patient to 30–32°C during cardiac anoxia and then rewarm to 36–37°C (bladder) before separation from CPB. For the experimental group the patients were cooled to 34°C on commencement of CPB and the perfusionists were asked to keep bladder temperature at that level through to termination of CPB. Blood warmers and heating blankets were not used intra- or postoperatively. Tympanic, nasopharyngeal, and bladder temperatures were recorded at five-minute intervals from the beginning of CPB until the patient left the operating room. Anaesthesia was induced with midazolam 0.03–0.10 mg · kg⁻¹ and sufentanil 1–3 µg · kg and maintained with infusions of midazolam and sufentanil, and inhaled isoflurane. Total sufentanil dose was usually < 5 µg · kg⁻¹. In the recovery room nasopharyngeal, pulmonary artery and bladder temperatures were recorded every 15 min for two hours and then hourly for another ten hours. Intraoperative blood loss was estimated using sponge weights and measurements of volumes in the suction and autotransfusion canister. However, this does not include blood returned to the pump via the cardiectomy suction. Postoperative blood loss was estimated from the volume collected from the mediastinal and chest tubes into the autotransfusion system which consisted of a two-litre canister containing 3000 units of heparin. The use of blood products and vasoactive drugs was noted. Postoperative shivering was graded: 1 = barely detectable, 2 = definite, 3 = vigorous. Muscle relaxants were prescribed at the discretion of the attending physician. Diagnosis of perioperative myocardial infarction required the appearance of new Q-waves 40 or more msec in duration and 25% of the R-wave in two contiguous leads. The CK MB fraction was not measured routinely. Left ventricle class was assessed on the preoperative ventriculogram in the right anterior oblique projection. The ventricle is divided into four segments and the class is the number showing akinesis.

Statistical analysis

Continuous variables were compared using *t* tests for independent samples or, when not normally distributed, using the Wilcoxon rank sum test. Categorical variables were compared using Fisher's exact test.

Results

The patients in the two groups were similar in age, ventricular function, aspirin use, and other preoperative char-

TABLE I Patient characteristics

	Control	Experimental
<i>n</i>	15	15
Age (mean ± SD)	63 ± 10	63 ± 9
Sex		
– Male	12 (80%)	12 (80%)
– Female	3 (20%)	3 (20%)
Aspirin	9 (60%)	14 (93%)
LV class		
– 1	4 (26.5%)	6 (40%)
– 2	1 (7%)	3 (20%)
– 3	4 (26.5%)	3 (20%)
– 4	1 (7%)	0
– Normal	5 (33%)	3 (20%)
CABG	14 (93%)	15 (100%)
Valve	1 (7%)	0

Patient characteristics did not differ between groups.

TABLE II Intraoperative characteristics

	Control	Experimental
<i>n</i>	15	15
Maximum tympanic temperature on CPB (°C, mean ± SD)	37.0 ± 0.70*	34.4 ± 0.41
CPB time (minutes, mean ± SD)	93.5 ± 21.9	103 ± 24.5
Aortic cross-clamp time (minutes, mean ± SD)	52.1 ± 14.4	51.4 ± 14.9
Tranexamic acid given	2	2
Inotropes required	4	3
Blood loss (ml, mean ± SD)†	1605 ± 2089	800 ± 514
Blood loss (ml, median)	1070	723
Packed RBC transfused (units, mean ± SD)	1.0 ± 2.4	0.93 ± 1.3
Number of patients receiving:		
– Packed RBC	5	7
– Plasma	1	0
– Cryoprecipitate	1	0
– Platelets	1	0

**P* < 0.001 compared to experimental group. No other differences reached statistical significance.

†One patient in control suffered massive haemorrhage after an anaphylactoid reaction to protamine.

acteristics (see Table I). There was no difference in time on CPB or duration of cardiac anoxia (Table II). In only three patients in the control group did tympanic temperatures exceed 38°C and the highest temperature reached during rewarming was 38.4°C (Figure 1). The NP temperature was consistently higher than tympanic temperatures during rewarming (Figure 2). The maximum difference occurred in the first 15 min of rewarming with a peak difference of 1.44 ± 0.29°C (mean ± SEM).

FIGURE 1 Tympanic temperatures during CPB.

FIGURE 2 Nasopharyngeal-tympenic temperature differences during rewarming in the control group (mean $\pm$ SEM).

In individual patients this difference sometimes exceeded 3°C.

Two patients in each group received tranexamic acid and the use of inotropes was similar in each group. Although not reaching statistical significance, mean intraoperative blood loss (Table II) was mathematically greater

FIGURE 3 The time course of spontaneous rewarming in the recovery room (mean $\pm$ SD).

TABLE III Postoperative bleeding

	Control	Experimental
Haematologic variables on arrival in recovery room (mean $\pm$ SD)		
- Haemoglobin ($\text{g} \cdot \text{L}^{-1}$)	96 $\pm$ 20	99 $\pm$ 13
- INR	1.28 $\pm$ 0.17	1.23 $\pm$ 0.17
- PTT (seconds)	33.3 $\pm$ 4.9	35.1 $\pm$ 0.07
- TT (seconds)	18.3 $\pm$ 4.0	18.4 $\pm$ 3.9
- Fibrinogen ($\text{g} \cdot \text{L}^{-1}$)	1.80 $\pm$ 0.58	1.78 $\pm$ 0.46
Blood loss in first 12 hours (ml)	787 $\pm$ 402	1057 $\pm$ 512
Packed RBC transfused (units)	0.86 $\pm$ 1.5	0.80 $\pm$ 1.3
Plasma (units)	0.29 $\pm$ 1.1	0.60 $\pm$ 1.1
Platelets (units)	1.7 $\pm$ 4.6	1.7 $\pm$ 3.1
Cryoprecipitate	1.4 $\pm$ 5.4	1.3 $\pm$ 5.2
Number of patients receiving		
- Packed RBC	5	5
- Plasma	1	4
- Platelets	2	4
- Cryoprecipitate	1	1

No statistically significant differences between the two groups.

in the control group, in part because of massive haemorrhage in one patient following an anaphylactoid reaction to protamine. Similar numbers of patients received packed red blood cell transfusions in the two groups.

On arrival in the recovery room mean bladder temperatures were $35.4 \pm 0.58^\circ\text{C}$ and $33.8 \pm 0.45^\circ\text{C}$ (mean $\pm$ SD, $P < 0.05$) in the control and hypothermic groups respectively (Figure 3). The control group on average reached 37°C after five hours compared with 9.5 hours for the hypothermic group. Heating blankets were not used in either group. The lowest temperature reached by a patient in the hypothermic group was 33.1°C .

Patients arrived in the recovery room with similar haemoglobin values and coagulogram (Table III). Mean

TABLE IV Early postoperative cardiac morbidity (first 24 hours postoperatively)

	Control	Experimental
<i>Number of patients</i>		
Receiving inotropes	6	7
Receiving vasodilators	11	12
Paced	0	2
With tachyarrhythmias	4	4
With bradyarrhythmias	1	2
Receiving antiarrhythmic drugs	3	2
Q-wave myocardial infarction	0	2

No significant differences between groups.

blood loss during the first 12 hr in the recovery room and blood product use was similar in the two groups during this period. Of the four patients receiving FFP in the hypothermic group all had INR values <1.4 ; two were not bleeding excessively but two returned to the OR for control of surgical bleeding. Three study patients returned to the OR for reexploration to control haemorrhage; all in the hypothermic group. In all three cases blood loss stopped after surgical bleeding sites were identified and controlled. The use of vasoactive drugs and the incidence of dysrhythmias (Table IV) were not different between groups. Two patients required pacing in the hypothermic group: one for 15 min following separation from CPB, and the other for 36 hr until complete heart block resolved.

The time from arrival in the recovery room to extubation was 19 ± 14 and 20.5 ± 4 hr (mean $\pm$ SD) in the control and hypothermic groups respectively. The large variation in the control group reflects one patient who required support from an intra-aortic balloon pump and the trachea was intubated for 65.7 hr. Median times were 18.2 hr in the control group and 19.8 hr ($P = \text{NS}$) in the hypothermic group. In two control patients and three hypothermic the tracheas remained intubated for more than 24 hr postoperatively. Nine patients in each group shivered (60%), the mean shivering grade (2 ± 0.5) was the same. Vigorous shivering (grade 3) was noted only in two patients, both in the hypothermic group. During the first 12 hr in the recovery room seven control patients received an average of 8.3 ± 2.1 mg vecuronium (mean $\pm$ SD), compared with ten who received 13.4 ± 6.6 mg in the hypothermic group ($P < 0.05$).

There were two perioperative Q-wave myocardial infarctions in the hypothermic and none in the control group ($P = 0.48$, Fisher's exact test). There were no deaths among the study patients.

Discussion

The main finding of this study was that prolonged mild

hypothermia did not cause increased morbidity following cardiac surgery. However, only 30 patients were enrolled and true differences may not have been detected (type II error). In particular, the great variability in bleeding between patients in the same group as well as the distinction between "medical" and "surgical" bleeding make it difficult to interpret blood loss data confidently. The three study patients who required reexploration for postoperative haemorrhage were in the hypothermic group. In each case, surgical bleeding site was identified and controlled after which there was no further bleeding. There was no difference between groups in the coagulogram obtained after arrival in the recovery room. Coagulation tests were performed at 37°C rather than at the temperature of the hypothermic patient. It has been demonstrated^{5,6} that when PT or PTT is measured at 34°C there is a small (11%) increase compared with measurements at 37°C . Platelet quantity and function were unaffected.⁶ The clinical importance of these findings are uncertain. The present data suggest that hypothermia did not contribute to postoperative blood loss. Nevertheless, larger studies are required to establish this fact.

The two patients graded as shivering vigorously were in the hyperthermic group and the number of patients receiving relaxant and the mean dose of relaxant were higher in that group. This suggests that, although the incidence of shivering was the same, the vigour of shivering was greater among hypothermic patients. If these findings were indeed due to hypothermia and not chance this complication could be addressed using surface warming in the recovery room. There was little decrease in temperature in the hypothermic group after separation from CPB. This is in part because their temperature was kept near 34°C throughout the CPB period. If patients were cooled further during CPB and then rewarmed to 34°C a greater "afterdrop" in temperature might be expected.

The present results agree with previous studies. Mild hypothermia ($32\text{--}35^\circ\text{C}$) is considered safe in that heat production and conservation remain intact. Complications of hypothermia, such as cardiac arrhythmias, altered drug metabolism, changes in acid base status and respiratory function, and changes in mental functioning are rarely observed at temperatures above 32°C .^{4,7,8}

The duration of action and recovery time after administration of muscle relaxant⁹ has been shown to be prolonged in patients at 34.5°C . Joachimsson *et al.*¹⁰ compared a group of patients that had extended rewarming on CPB to mean rectal temperatures of 36.8°C with a group who separated from CPB with a mean rectal temperature of 33.8°C . The incidence as well as intensity of shivering was less in the warm group. Differences in haemodynamics and oxygen transport between groups

were not sufficiently large to reach statistical significance. This may be explained in part because, by the time the patients left the operating room, rectal temperature had increased to 35°C in the control group, and decreased to 36.4°C in the warm group. There were no differences in blood loss or fluid requirements.

Baker *et al.*¹¹ studied the safety of mild intraoperative hypothermia in 30 patients without known heart disease undergoing craniotomy. Fifteen patients were surface cooled to a tympanic temperature of 34.5°C and rewarmed at the end of surgery. It proved impossible to rewarm the hypothermic patients completely so that on arrival in the intensive care unit the mean temperature in the cool group was 35.8°C compared with 37.1°C in the normothermic group. Other than an increased incidence of shivering there were no complications attributable to hypothermia. Frank *et al.*¹² studied 100 patients undergoing lower extremity vascular surgery, a population known to have a high incidence of coronary disease. They found a higher incidence of ST-segment depression (36 vs 13%), and angina (18 vs 1.5%), and PaO₂ < 80 mmHg (52 vs 30%) in patients whose sublingual temperature had unintentionally reached <35°C by the time of arrival in intensive care. Although the hypothermic group was older there was a relationship between temperature and myocardial ischaemia even after correction for age. There were no differences between groups in shivering, haematocrit, myocardial infarction and major morbidity. Increased vigilance would be required if patients with uncorrected coronary artery disease are subjected to controlled hypothermia extending into the postoperative period.

The fact that nasopharyngeal temperature exceeded tympanic temperature during rewarming suggested to us that NP better reflects the brain temperature. This interpretation is supported by the recent findings of Stone *et al.*¹³ who compared temperature measured from a probe in the cerebral cortex with probes at other sites including the tympanic membrane and nasopharynx. Brain temperature exceeded tympanic temperature by a larger amount than nasopharyngeal temperature during rewarming on CPB. It is noteworthy that, during rewarming, brain temperature was more than 2°C higher than temperature measured at the other two sites.

Our findings suggest that mild hypothermia following CPB does not increase morbidity and, if proved effective, could be used safely as a strategy for neuroprotection. Larger studies are needed to confirm that hypothermia does not increase postoperative blood loss.

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