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Normothermic cardiopulmonary bypass and cardioplegia reduce inotropic requirements and creatine kinase-MB after coronary artery bypass graft surgery

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Abstract
Purpose. To determine whether normothermic cardiopulmonary bypass (CPB) and cardioplegia preserve myocardial function, reduce inotropic requirements, and reduce markers of myocardial ischemia following coronary artery bypass graft surgery (CABG).
Methods. We retrospectively reviewed the charts of 171 consecutive patients undergoing elective CABG by a single surgeon from April 1994 to December 1995. Hypothermic CPB with intermittent cold cardioplegia was used in 83 patients and normothermic CPB with intermittent warm cardioplegia in 88 patients. Demographic, surgical, hemodynamic, and inotropic requirements and laboratory data were reviewed.
Results. The duration of CPB was significantly shorter in the normothermic group (113 ± 27 *vs* 90 ± 21 min; $P < 0.0001$). After CPB the cardiac index was similar between groups, but significantly larger doses of both dopamine and dobutamine were required (8 *vs* 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$; $P < 0.0001$), and significantly more patients required norepinephrine administration in the hypothermic group (18% *vs* 6%; $P = 0.01$). Postoperative peak values of creatine kinase MB fraction (CK-MB) were significantly lower in the normothermic group (80 ± 60 *vs* 55 ± 54 $IU \cdot l^{-1}$; $P < 0.0001$).
Conclusion. Normothermic CPB and cardioplegia reduce inotropic requirements and CK-MB following CABG.

Key words: Normothermia, Cardiopulmonary bypass, Cardioplegia

Introduction

Hypothermic cardiopulmonary bypass (CPB) has been used in cardiac surgery to facilitate myocardial and cerebral preservation. Recently it was demonstrated that normothermic CPB and cardioplegia improved post-CPB cardiac function, reduced the incidence of perioperative myocardial infarctions (MI), and reduced the incidence of low-output syndromes and the need for intraaortic balloon counterpulsation (IABP) [1]. Normothermic CPB and cardioplegia also resulted in a reduction in markers of myocardial ischemia [2,3]. However, in contrast, other studies have not reported a corresponding reduction in myocardial ischemia or MI [4–7]. We hypothesized that normothermic CPB and cardioplegia would preserve myocardial function, reduce inotropic requirements, and reduce markers of myocardial ischemia following coronary artery bypass graft surgery (CABG).

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Materials and methods

After Institutional Review Board approval, we retrospectively reviewed the medical records of 171 consecutive patients undergoing elective CABG by a single surgeon from April 1994 through December 1995. Patients with a calcified ascending aorta that could not be cross-clamped, repeated CABG, or combined surgery for valvular disease were not included. Hypothermic CPB and intermittent cold cardioplegia were used in 83 patients, and 88 patients received normothermic CPB and intermittent warm cardioplegia.

Premedication with diazepam, 10 mg, po, and morphine, 5–10 mg, im, was administered to all patients. Radial artery and pulmonary artery catheters were inserted before induction of anesthesia. Anesthesia was induced with fentanyl, 10–30 $\mu g \cdot kg^{-1}$, midazolam, 0.1–0.2 $mg \cdot kg^{-1}$, and pancuronium, 0.1–0.15 $mg \cdot kg^{-1}$. Anesthesia was maintained with midazolam, pancuronium, and inhaled isoflurane. Bladder temperature was continuously monitored with a thermal sensor-equipped catheter, and nitroglycerin was administered at 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ before CPB. Prostaglandin E_1 was also administered at 0.02–0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in most cases

(70 cases in the hypothermic group *vs* 75 cases in the normothermic group).

After median sternotomy, the cardiac surgeon evaluated the aortic calcification by palpation and periaortic echocardiography. The ascending aorta was cannulated and cross-clamped in the standard fashion. If clinically significant aortic calcification was present, an arterial cannula was inserted via the femoral artery. CPB was instituted at a flow rate of $2.6\,l\,min^{-1}\cdot m^{-2}$ and perfusion pressure between 50 and 60 mmHg with phenylephrine and/or chlorpromazine administration if necessary. The patients were cooled to a bladder temperature of 27–28°C in the hypothermic group or maintained at 36–37°C in the normothermic group. During CPB, $PaCO_2$ was maintained between 30 and 40 mmHg in both groups (uncorrected in the hypothermic group). Antegrade potassium and oxygenated blood cardioplegia was infused at 4°C in the hypothermic group and at 36°C in the normothermic group immediately after aortic cross-clamping and at 30-min intervals thereafter. In the hypothermic group, 1 mg chlorpromazine was added to the cardioplegic solution and slushed ice/water was applied to the pericardial wall. Just before removal of the aortic cross-clamp, terminal cardioplegia was infused at 36°C in the hypothermic group only.

Discontinuation of CPB was carried out in the standard fashion, with routine administration of both dopamine and dobutamine (DOAB) to maintain the cardiac index (CI) greater than $3\,l\,min^{-1}\cdot m^{-2}$, mixed venous saturation greater than 70%, systemic blood pressure greater than 90 mmHg, and adequate urinary output. Norepinephrine was administered if required.

Table 1. Demographic data on patients; mean ± SD

Characteristic	Hypothermic CPB	Normothermic CPB
Number of cases	83	88
Age (yr)	65 ± 8	65 ± 8
Sex (male:female)	59 : 24	60 : 28
Height (cm)	158 ± 8	157 ± 10
Weight (kg)	59 ± 8	59 ± 8
Left main stenosis	39 (47%)	45 (51%)
3-vessel disease	50 (60%)	60 (68%)
Prior MI	42 (51%)	37 (42%)
EF (%)	61 ± 13	62 ± 13

CPB, Cardiopulmonary bypass; MI, myocardial infarction; EF, ejection fraction.

The operative variables recorded included the duration of the operation and of aortic cross-clamp, and the number of anastomoses. CPB measurements included bladder temperature, duration of CPB, perfusion pressure, and total dose of phenylephrine, chlorpromazine, and cardioplegia. The hemodynamics with inotropic agents administered on discontinuation of CPB and upon sternal closure, and the numbers of countershocks required after CPB, were also noted.

In the postoperative period, the peak value of creatine kinase-MB isozyme (CK-MB), the incidence of perioperative MI, and mortality were noted. CK-MB was measured six times every 3 h after admission to the

Table 2. Intraoperative data on patients; mean ± SD or median [range]

Data	Hypothermic CPB (n = 83)	Normothermic CPB (n = 88)
Operative management		
Surgical procedure (min)	326 ± 70	297 ± 66*
Cross-clamping (min)	74 ± 22	64 ± 16*
No. of anastomoses per patient	3 [0[a]–6]	4 [2–6]
CPB management		
Bladder temperature (°C)	27.9 ± 0.9	36.7 ± 0.3**
Duration (min)	113 ± 27	90 ± 21**
Perfusion pressure (mmHg)	59 ± 10	58 ± 11
Phenylephrine (mg)	0 [0–10]	2.75 [0–20]**
Chlorpromazine (mg)	0 [0–20]	0 [0–13]*
No. of cardioplegias per patient	3 [2–5]	2 [1–3]**
Total cardioplegia (ml)	2449 ± 524	1331 ± 366**
Anesthetic agents		
Fentanyl (μg)	1537 ± 563	1643 ± 484
Midazolam (mg)	27 ± 8	19 ± 7**
Pancuronium (mg)	17 ± 3	17 ± 4

*$P < 0.01$; **$P < 0.0001$.
CPB, Cardiopulmonary bypass.
[a]Patch plasty for left main stenosis was included in the hypothermic group.

Table 3. Hemodynamic data on patients; mean ± SD or median [range]

Data	Hypothermic CPB (n = 83)	Normothermic CPB (n = 88)
Cardiac function and inotropic requirements		
Preinduction		
CI ($l \cdot min^{-1} \cdot m^{-2}$)	3.2 ± 0.7	3.5 ± 0.8
Post-CPB		
CI ($l \cdot min^{-1} \cdot m^{-2}$)	3.8 ± 0.7	4.0 ± 0.8
DOAB ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	8 [4–10]	5 [2–10]**
Mean SBP (mmHg)	69 ± 9	68 ± 13
Mean PBP (mmHg)	15 ± 2	16 ± 3
Sternal closure		
CI ($l \cdot min^{-1} \cdot m^{-2}$)	3.8 ± 1.0	3.9 ± 1.0
DOAB ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	5 [2–10]	3 [0–8]**
Mean SBP (mmHg)	78 ± 10	79 ± 12
Mean PBP (mmHg)	17 ± 3	17 ± 3
No. of countershocks per patient after CPB	0 [0–4]	0 [0–3]
No. (%) of patients with norepinephrine infusion	15 (18%)	5 (6%)*

* $P < 0.05$; ** $P < 0.0001$.
CPB, Cardiopulmonary bypass; CI, cardiac index; DOAB, both dopamine and dobutamine; SBP, systemic blood pressure; PBP, pulmonary blood pressure.

intersive care unit, and then three times every 6 h. The diagnosis of MI required new Q waves that were at least 40 ms in duration and a new R wave greater than 25%.

All data were analyzed by the chi-square test, the unpaired t-test, or the Mann-Whitney U test, as appropriate. Differences were considered statistically significant if P values were less than 0.05.

Results

Preoperative characteristics are summarized in Table 1. The hypothermic and normothermic groups did not differ in age, sex, height, or weight; incidence of left main stenosis, three-vessel disease, or prior myocardial infarction; and ejection fraction. A fairly large proportion of patients had severe coronary disease. This was not due to patient selection but rather resulted from the type of clinical practice in our hospital. The specific surgical procedures performed did not differ between the two groups. The durations of aortic cross-clamp and the procedure were significantly longer in the hypothermic group.

Regarding CPB management, the bladder temperature and duration of CPB were significantly lower and longer, respectively, in the hypothermic group. The perfusion pressure of CPB did not differ between the groups, with significantly more phenylephrine and less chlorpromazine administration in the normothermic group. The frequency of cardioplegia infusion and the total dose of cardioplegia were both significantly lower in the normothermic group, because the terminal warm cardioplegia before to aortic declamp was used only in the hypothermic group. No significant differences in the doses of fentanyl and pancuronium were seen, whereas the total midazolam required was less in the normothermic group (Table 2).

The hemodynamic data are summarized in Table 3. There was no difference between the two groups in the cardiac index before induction of anesthesia, immediately post-CPB, and at sternal closure. There was also no difference in the mean systemic and pulmonary artery blood pressure after CPB. However, the inotropic agent requirements were significantly lower in the normothermic group after CPB. Furthermore, fewer patients in the normothermic group required norepinephrine. No patient in either group needed IABP. The frequency of countershocks after aortic declamp and the incidence of spontaneous beating [n = 60 (72%) *vs* n = 66 (75%)] were similar in both groups.

In the normothermic group, postoperative peak CK-MB was significantly lower, and there was a trend toward a lower incidence of perioperative MI [n = 9 (10.8%) *vs* n = 4 (4.5%); P = 0.10]. There were no operative deaths in either group (Table 4).

Discussion

This study demonstrates that normothermic CPB is associated with improved myocardial preservation, as indicated by reduced peak CK-MB levels and reduced inotropic requirements when compared with hypothermic CPB. Lichtenstein and others [1] have described improved myocardial preservation, reduced incidence

Table 4. Postoperative data on patients; mean ± SD or median [range]

Data	Hypothermic CPB (n = 83)	Normothermic CPB (n = 88)
CK-MB peak ($IU \cdot l^{-1}$)	80 ± 60 58 [28–724]	55 ± 54* 38 [13–330]
No. (%) of patients with perioperative MI	9 (10.8%)	4 (4.5%)**
No. (%) of patients who died	0 (0%)	0 (0%)

* $P < 0.05$; ** $P = 0.10$.
CK-MB, Creatine kinase isozyme MB; MI, myocardial infarction.

of MI, and reduced incidence of IABP in patients undergoing normothermic CPB. Elimination of the hypothermic injury inherent with conventional cold techniques may account for these better results.

However, large, randomized trials have demonstrated reduced enzymatic reactions in normothermic CPB [2,3], and other studies have failed to confirm that normothermic CPB reduces enzymatic reactions [4–7]. This controversy deserves comment. Among the procedures that imply warm-heart surgery, there are many differences in CPB flow and perfusion pressure and, in regard to cardioplegia, in its content (blood or crystalloid) and its manner of injection (antegrade or retrograde, continuous or intermittent). Furthermore, skeletal muscle injury induced during surgery may increase the postoperative concentration of CK-MB; therefore, a variety of surgical techniques decrease CK-MB specificity for myocardial ischemia.

In the present study, we controlled the temperature of systemic and coronary perfusion at 36°C in the normothermic group and used the same intermittent blood cardioplegia in both groups. This study confirmed that normothermic CPB and cardioplegia reduced enzymatic reactions. In laboratory investigations, blood cardioplegia infused at 20°C preserved left ventricular function better than cardioplegia infused at 4°C. Yet crystalloid cardioplegia infused at either 4°C or 10°C was as effective in myocardial preservation as blood cardioplegia at 20°C [8].

We achieved good myocardial preservation with intermittent cardioplegia, which confirms the findings of others [3]. Lichtenstein [1] employed continuous cardioplegic techniques with similar success. It seems that continuous or intermittent cardioplegia does not affect myocardial preservation with normothermic management in this setting.

It has been shown with normothermic CPB compared with hypothermic CPB that further reduction of systemic vascular resistance increases cardiac output after CPB [7]. However, at the start of normothermic CPB, we ceased to use chlorpromazine in the cardioplegia to prevent excessive vasodilation during normothermic CPB; more phenylephrine and less chlorpromazine were needed to maintain the target perfusion pressure in the normothermic group. There was no difference between the groups in the method of continuous infusion of nitroglycerin and prostaglandin E_1.

This retrospective analysis was completed on consecutive patients undergoing elective CABG with a single surgeon during a specific interval when the only change instituted in perioperative care was normothermic CPB and cardioplegia. Although the duration of cross-clamping was coincidentally shorter in the normothermic group (74 ± 22 *vs* 64 ± 16 min; $P = 0.0019$), the nature of the surgical procedures was similar (number of anastomoses and grafts, etc.). It seems that the terminal warm cardioplegia employed only in the hypothermic group partly resulted in the different durations of cross-clamping. The standards of anesthetic care did not change during the study interval without the more rapid extubation philosophy employed in the normothermic group, which was also reflected in the reduced dose of midazolam.

The observed reduction in inotropic requirements in the normothermic group likely resulted from improved myocardial preservation and lower systemic vascular resistance. The reduced duration of CPB likely resulted from the elimination of the need for rewarming and also improved hemodynamics.

Because it is not clear whether moderate hypothermia during CPB can lessen central nervous system (CNS) complications after cardiac surgery, controversy exists about the neurological outcome after normothermic CPB [2,4]. We recently reported that there were no significant differences between hypothermic and normothermic CPB (4.1%, n = 122 *vs* 2.3%, n = 128; $P = 0.43$) with almost the same patient selection and exclusion criteria [9]. It has been shown that CNS complications after cardiac surgery may be due mainly to atheroemboli from atherosclerosis and surgical manipulation [10]. We suspect that the patient subset in our study had slight abnormalities of the

ascending aorta available for cross-clamping, and the changes in perfusion temperature during CPB had no significant effect on the incidence of CNS complications.

We conclude that normothermic CPB and cardioplegia, as compared with hypothermic management, was associated with improved myocardial preservation and reduced inotropic requirements following CABG. Further investigation of the various modalities of normothermic CPB and cardioplegia is warranted.

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