Original Article

The Effect of Temperature Management During Cardiopulmonary Bypass on Clinical Outcome in Pediatric Patients Undergoing Correction of Ventricular Septal Defect

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ABSTRACT

Moderate hypothermia of 28°C is widely accepted in cardiac surgery with cardiopulmonary bypass (CPB). Recently, however, several studies suggested that normothermic or "tepid" bypass techniques may improve the clinical outcome for patients undergoing cardiac operations.

To assess the effect of bypass temperature management strategy in pediatric patients undergoing correction of ventricular septal defect, 26 patients with body weight under 10 kg were randomly assigned to two treatment groups: Group 1, mild hypothermia, patients cooled to nasopharyngeal temperature of 32°C during the bypass; or Group 2, moderate hypothermia of 28°C. Clinical parameters were recorded, and blood samples were obtained just before, during, and 24 hours after operation.

All the population characteristics and intraoperative variables were similar in the two groups. Hematologic data after CPB and protamine administration revealed a significantly ($p < .05$) longer activated partial thromboplastin time in the 32°C group; however, the difference in blood loss did not reach significance. Our study shows that both perfusion temperatures equally well facilitated CPB for this type of intracardiac surgery.

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INTRODUCTION

Until recently, intracardiac repair in pediatric cardiac surgery was mostly performed with moderate (27–30°C) to profound (<25°C) systemic hypothermia. The exceptions to this rule were short procedures for which only mild (30–32°C) hypothermia was used.

Systemic hypothermia reduces tissue metabolic rate and oxygen demand and is used to protect the myocardium and the brain against potential ischemic insult (1–3). Furthermore, it enhances protection of the other organs. Systemic hypothermia allows us to lower the arterial blood flow and promotes better conditions in the operation field as well as less blood trauma occurrence. Hypothermia also causes marked changes in the peripheral circulation, hormonal body response, and alterations in organ function. Generalized inflammatory response, involving the complement, coagulation, kallikrein and fibrinolytic cascades, is often a dominant feature of hypothermic bypass (4–6). Undoubtedly, hypothermia has its positive as well as negative aspects during cardiopulmonary bypass (CPB). Therefore, normothermic CPB with warm cardioplegia in adult cardiac surgery is becoming increasingly popular (7). In pediatric heart surgery, technical developments and enhanced surgical skills also allow for reduction of depth of hypothermia in most procedures. Nevertheless, comparatively few publications have addressed the issues raised by maintenance of mild or moderate hypothermia during pediatric bypass. The aim of this study was to compare clinical results between two groups of pediatric patients, operated with short aorta occlusion times and mild or moderate hypothermic CPB.

MATERIALS AND METHODS

Patients

The study population comprised 26 consecutive pediatric patients who underwent closure of ventricular septal defect (VSD) with use of a Gore-Tex®[a] patch. Only children with body weight under 10 kg and without concomitant heart disease were included. Exclusion criteria were: respiratory insufficiency with need of respiratory support; kidney failure; liver failure; and neurological impairment. Patients were equally randomized into two groups: Group 1, mild hypothermia (nasopharyngeal temperature ≥32°C during CPB); Group 2, moderate hypothermia (nasopharyngeal temp. ≥28°C during CPB). All operations were performed by one surgeon. The study was conducted according to the regulations of the hospital medical ethical committee. Informed parental consent was obtained for all patients.

Anesthesia

Patients were premedicated with 0.3 mg/kg midazolam suppositorium 1 h before induction of anesthesia. Induction of anesthesia was done by inhalation (halothane or sevoflurane) or intravenously (midazolam, pavulon, fentanyl). Patients were intubated with a nasal–endotracheal tube and ventilated with a minute volume of 10 mL/kg/min.

Heart rate, ECG, arterial and right atrial blood pressure, nasopharyngeal and rectal temperature were continuously measured. A bladder catheter was inserted to monitor urine production during and after the operation.

Cardiopulmonary Bypass

All patients were operated upon with CPB and cardioplegic arrest. In all patients, the ascending aorta was cannulated with either an 8 or 10 Fr. standard straight-tip cannula, depending upon patient size. In all cases, venous return was provided by bicaval cannulation of the superior and inferior caval veins with angled metal tip 12 Fr. cannulae.

CPB circuit consisted of a membrane oxygenator with integrated venous-cardiotomy reservoir,[b] roller pump with silicone tubing and an arterial line filter.[c] The circuit was primed with Ringer's solution[d] and whole blood to achieve an intraoperative hematocrit of 28% during the bypass period. During CPB, nonpulsatile pump flow with rates of 1.8–2.4 L/min/m^2 was maintained adequate to the metabolic needs of the patient. In-line monitoring of arterial oxygen tension (PaO_2) and venous oxygen saturation (SvO_2) provided conditions for alpha-stat strategy during the whole period of bypass.

Anticoagulation of the patient and the CPB circuit were achieved with initial patient heparin[e] dose of 300 IU/kg body weight and prime heparin dose of 4.2 IU/mL total prime volume. Assessment of anticoagulation during operation was done by measurement of the kaolin activated clotting time (ACT).[f] The ACT values were maintained ≥480 sec by administration of additional heparin when necessary. After discontinuation of the CPB, heparin was neutralized by protamine chloride[g] with a standard dose of 4 to 5 mg/kg body weight. Adequacy of protamine reversal was ascertained with the use of heparin–protamine titration.[h] No aprotinin was administrated to patients in the study population.

Patient mean arterial blood pressure was maintained between 30–65 mmHg during the bypass. Continuous recording of the pump flow, arterial blood temperature, along with patient nasopharyngeal and rectal temperatures, oxygen and air flow, PaO_2, SvO_2, arterial line pressure, as well as patient pressures, was provided by "Odis," a perfusion registration system (8, 9).

a V.L. Gore, Flagstaff, AZ

b VPCML—0.85 m^2, Cobe Cardiovascular Inc., Arvada, CO
c D 736, Dideco, Mirandola, Italy
d Baxter, Utrecht, The Netherlands
e Leo Pharm., Weesp, The Netherlands
f HemoTec ACT, Medtronic Inc., Annaheim, CA
g Kabi Pharm., Woerden, The Netherlands
h Hemostasis Management System, Medtronic Cardiopulm., Engelwood, CO

Myocardial preservation was achieved by antegrade administration of cold (4°C) St. Thomas Hospital cardioplegic solution delivered by gravity at the dose of 10–15 mL/kg of body weight after application of the aortic cross clamp. No topical cooling was used. All patients were weaned from bypass with infusion of dopamine 2 μg/kg/min and nitroglycerin 1 μg/kg/min.

MEASUREMENTS AND CALCULATIONS

In both groups, arterial and venous blood gas samples were obtained before bypass, during CPB after 5 min, 20 min, and at the end (±50 min). The last sample was obtained after administration of protamine chloride. During CPB, oxygen consumption index ($V_{O_2}I$) and systemic vascular resistance (SVR) were calculated as follows:

$$\text{SVR} = [(\text{mean arterial pressure} - \text{central venous pressure})/\text{cardiac output}] \times 80 \text{ dynes sec cm}^{-5}$$

$$\text{Vo}_2\,\text{I} = \text{cardiac index} \times [(\text{art. saturation} - \text{ven. saturation}) \times \text{Hgb} \times 2.32]\ \text{mL/min m}^2$$

Coagulation factors were platelet count, fibrinogen, activated partial thromboplastic time (APTT), and thrombin time (TT), which were measured before the bypass, after protamine chloride administration, and 24 hours after the operation.

Other measured and recorded variables include: occurrence of electrical activity (ECG) during the aortic cross clamping, spontaneous cardiac conversion after releasing of the clamp, and existence of any sort of rhythm disturbances. Also, the amount of administrated blood products, diuresis, blood loss, length of the respiratory support, and stay in the intensive care unit (ICU) were recorded.

Intraoperative postcorrection epicardial echocardiography (10) was carried out with color-Doppler studies to assess left-to-right shunting by echo-contrast injection into the left atrium. After 24 hours postoperative, left ventricular function was determined by echocardiography and follow-up was completed at the discharge visit.

DATA ANALYSIS

All values are presented as mean ± standard deviation (SD) of the mean. Two-way analysis of variance (ANOVA) for repeated measurements was used for comparison between the groups at specific points in time. *p*-Values were obtained for the over-all group effect. Other data were compared by paired *t*-test between the two groups. *p*-Values ≤ 0.05 were considered statistically significant.

RESULTS

There were no significant differences in the baseline data between the two groups (Table 1). Mean nasopharyngeal (N) and rectal (R) temperatures after 5 min on CPB were not significantly different (Group 1; N: 32.5 ± 0.0 R: 33.0 ± 0.1 vs. Group 2; N: 31.9 ± 0.0 R: 33.2 ± 0.1°C, NS). After 20 min on bypass, a significance occurred (Group 1; N: 31.6 ± 0.0 R: 32.3 ± 0.1 vs. Group 2; N: 29.2 ± 0.0 R: 30.9 ± 0.0°C with $p = .008$ and $p = .01$, respectively). After 50 min on CPB and rewarming in progress, rectal temperature in Group 2 was still significantly lower (Group 1 R: 34.0 ± 0.1 vs. Group 2 R: 33.2 ± 0.0°C, $p = .02$), but nasopharyngeal temperatures were similar in the groups (Group 1; N: 35.8 ± 0.1 vs. Group 2; N: 35.3 ± 0.0°C, NS, Figure 1).

Hemodynamic parameters measured and calculated during CPB revealed no significant differences between recorded mean arterial pressure (Figure 2); on the other hand, the over-all cardiac index was significantly higher in mild hypothermia group (Group 1; 2.43 ± 0.2 vs. Group 2; 2.16 ± 0.2, $p = .02$, Figure 3).

During CPB, the moderate hypothermic group had significantly higher over-all systemic vascular resistance (Group 1; 1164 ± 389 vs. Group 2; 1703 ± 420 dyne sec cm^{-5}, $p = .04$, Figure 4). Oxygen consumption was not significantly different in both groups at the time of measurements (Figure 5). Venous oxygen saturation remained relatively steady in each group during the CPB period, and there was a significant difference between the groups only at the 5-min bypass time (Group 1; 75% vs. Group 2; 66%, $p = .01$, Figure 6).

Atrial electrical activity (P wave) during aortic cross clamping was observed in four patients in Group 1 and in one in Group 2 ($p = .04$). No action was taken in any of these situations. All patients in both groups converted spontaneously to sinus rhythm after aorta declamping. AV block was temporally observed in two patients in Group 1. The external pacing was applied before sinus rhythm returned.

Initial dose of heparin used before the start of CPB was not significantly different between both groups (Group 1; 1222 ±

Table 1: Characteristics and perfusion data of the study population

	Group 1, 32°C	Group 2, 28°C	*p*-value
Age (mo)	3.5 ± 1.6	5.0 ± 3.2	NS
Weight (g)	4250 ± 817	4958 ± 1245	NS
Height (cm)	56.8 ± 15.8	60.0 ± 4.5	NS
BSA (M2)	0.27 ± 0.03	0.30 ± 0.05	NS
Calc. Pump flow (mL/min)	641 ± 83	713 ± 116	NS
Mean pump flow (mL/min)	592 ± 12	597 ± 129	NS
CPB time (min)	54.5 ± 2.0	56.1 ± 16.0	NS
Crossclamp time (min)	31.5 ± 2.0	31.4 ± 15.0	NS
Cardioplegic sol. (ml)	65 ± 30	65 ± 18	NS

All values reported as mean ± SD; NS, not significant; CPB, cardiopulmonary bypass; calc. pump flow = BSA (dm2) × 24 (mL/min/dm2); mean pump flow = mean flow during CPB.

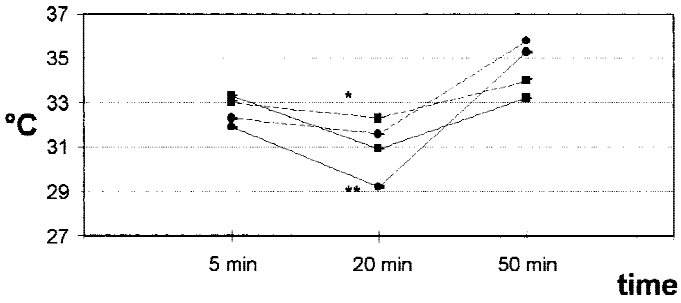

Figure 1: Changes of temperature during CPB.
---●--- Group 32°C—N — ○—Group 28°C—N
---■--- Group 32°C—R — ■—Group 28°C—R
***p = .01**
****p = .0008.**

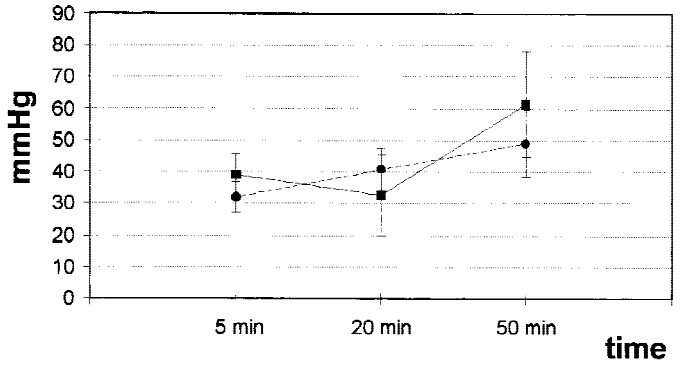

Figure 2: Mean arterial pressure during CPB.
---●--- Group 32°C —■—Group 28°C.

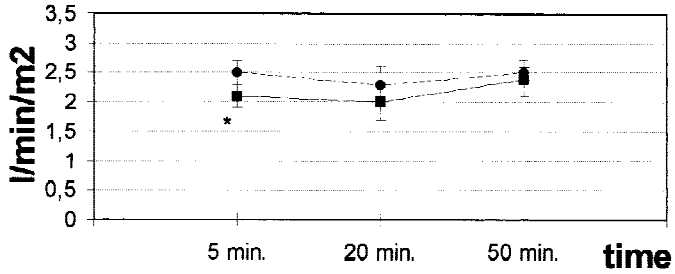

Figure 3: C.I. during CPB.
---●--- Group 32°C —■—Group 28°C
***p = .0006.**

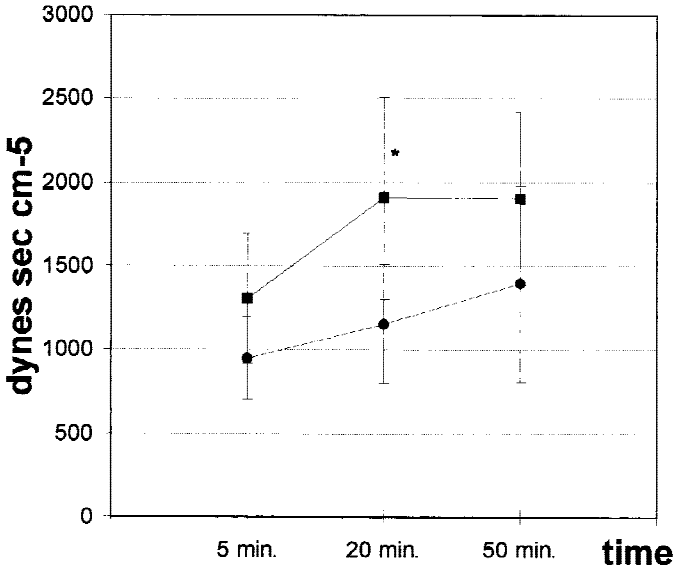

Figure 4: SVR during CPB.
---●--- Group 32°C —■—Group 28°C
***p = .01.**

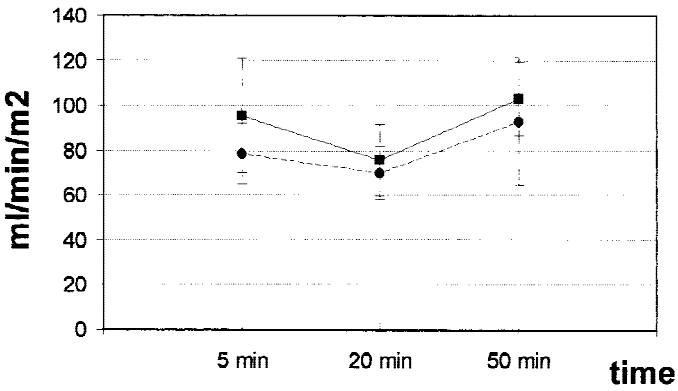

Figure 5: Oxygen consumption during CPB.
---●--- Group 32°C —■—Group 28°C.

290 vs. Group 2; 1500 ± 409 IU, NS). During CPB, two patients from Group 1 and one from Group 2 required additional heparin to sustain ACT ≥ 480 sec. Standard protamine dose given in compliance with protocol was not significantly different. In each group, four patients required additional protamine (Group 1; 2.2 ± 3.4 mg. vs. Group 2; 2.4 ± 3.5 mg, NS). Preoperative measurement of coagulation factors as well as baseline ACT in both groups were not significantly different. After administration of protamine, the ACT values were still higher if compared with baseline values but did not show any significant difference between groups; whereas, APTT values (Group 1; 55 ± 18 vs. Group 2; 41 ± 3 s, $p = .045$) were significantly higher in mild hypothermia group (Table 2). There was no difference in diuresis, blood loss, and the amount of blood products used during the period of 24 hours post CPB (Table 3).

Also, the mean duration of postoperative ventilatory support as well as the highest percentage of oxygen used in inspiratory fraction (FiO_2%) and applied positive end expiratory pressure (PEEP) were similar (Table 4). The mean duration of stay at the ICU by patients in both groups was not significantly different.

Intraoperative epicardial echocardiography revealed a residual VSD with insignificant leakage of contrast in two pa-

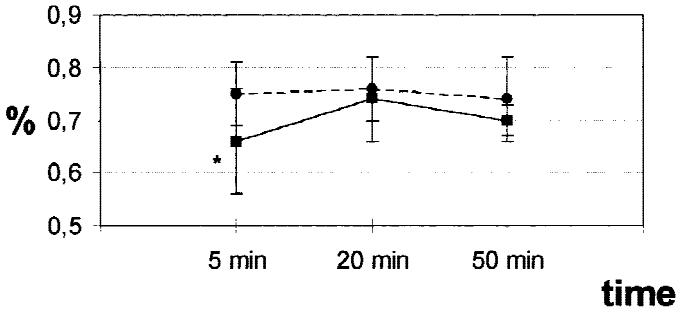

Figure 6: SvO_2 during CPB.
—■—Group 28°C --- ●--- Group 32°C
***p* = .01.**

Table 2: ACT values and plasma coagulation factors pre- and post-CPB

	Group 1, 32°C	Group 2, 28°C	*p*-value
Pre CPB			
ACT (sec)	127 ± 16	132 ± 9	NS
APTT (sec)	48 ± 11	51 ± 17	NS
APTT ratio	1.6 ± 0.4	1.7 ± 0.6	NS
TT (sec)	19 ± 7	16 ± 2	NS
Fibrinogen (mg/dL)	220 ± 70	220 ± 50	NS
Platelets (× 1000/mm^3)	287 ± 55	315 ± 78	NS
Post CPB			
ACT (sec)	144 ± 35	141 ± 23	NS
APTT (sec)	55 ± 18	41 ± 3	0,045
APTT ratio	1.5 ± 0.1	1.4 ± 0.1	NS
TT (sec)	15 ± 2	15.9 ± 3	NS
Fibrinogen (mg/dL)	160 ± 30	180 ± 40	NS
Platelets (× 1000/mm^3)	177 ± 61	183 ± 50	NS

All values reported as mean ± SD; NS, not significant. ACT, activated clotting time; APTT, activated partial thromboplastin time; APTT ratio, patient's APTT/normal population APTT; TT, thrombin time.

Table 3: Urine production and blood balance in 24 hours after CPB

	Group 1, 32°C	Group 2, 28°C	*p*-value
Urine excretion (ml)	345 ± 44	350 ± 111	NS
Blood loss (ml)	109 ± 106	95 ± 24	NS
Use of homologous blood (ml)	175 ± 39	145 ± 53	NS
Use of FFP (ml)	63 ± 117	106 ± 90	NS

All values reported as mean ± SD. NS, not significant; FFP, fresh frozen plasma.

tients from Group 1 and three patients from Group 2. At discharge, two patients in Group 1 displayed a hemodynamically insignificant residual VSD as well as one patient in Group 2. No residual VSDs were observed on subsequent follow-up visits. Intraoperative postcorrection epicardial echocardiography assessed left ventricular function in all patients as normal. Echocardiografic examination after 24 hours estimated left ventricular function as "diminished" in three patients in Group 1 and one patient in Group 2; nevertheless, at discharge, all patients regained normal left ventricular function.

Table 4: Postoperative use of the respiratory support

	Group 1, 32°C	Group 2, 28°C	*p*-value
Respiratory supp. (h)	22.8 ± 18	16.5 ± 19	NS
Highest FiO2 (%)	48.8 ± 11	46.0 ± 10	NS
PEEP (cm H2O)	3.5 ± 0.8	3.7 ± 1.0	NS

All values reported as mean ± SD. NS, not significant; FiO2, inspiratory fraction of oxygen; PEEP, positive end expiratory pressure.

DISCUSSION

Use of moderate (28°C) systemic hypothermia improves operating conditions and allows lower arterial flow rates. This, in turn, reduces collateral coronary circulation and contributes to myocardial protection as well as protection of other vital organs. Therefore, moderate hypothermia is widely carried out, although the effects of skin and, perhaps, muscle ischemia related to this temperature and the increased sympathetic effects may balance out any potential advantages (11). Another effect of hypothermia is that blood viscosity increases so that use of appropriate hemodilution is required to reduce the systemic vascular resistance during CPB (12). Hypothermia together with hemodilution disturbs coagulation and fibrinolitic cascades; this is assumed to be responsible for enhanced blood loss during and after operation (13). In certain operations, the selection of CPB temperature is dependent on the complexity of the operation; for example, deep hypothermia during circulatory arrest. Therefore, questions may be raised as to what the best temperature is in the case of short (under 1 h of CPB time) surgical procedures for small pediatric patients with body weight under 10 kg. (14). According to the surgeon's opinion, use of moderate (28°C) or mild (32°C) hypothermia during correction of the ventricular septal defect had no influence on the technical complexity of the operation.

The hemodynamic data obtained from both groups showed no differences in adequacy of the CPB. Mean arterial pressure and venous oxygen saturation were kept constant during the bypass without any difficulty, although patients from Group 1 −32°C required significantly higher CI to achieve this. On the other hand Group 2–28°C had significantly higher over-all systemic vascular resistance during the CPB, which might be caused by moderate hypothermia. Oxygen consumption in the two groups was not significantly different, which can be explained by the negligible differences of patient's temperatures during long times on CPB.

Myocardial protection in both groups was the same, and

there was spontaneous return of sinus rhythm in all the cases. In Group 1, −32°C atrioventricular block occurred twice, which had to be resolved by temporary use of a pacemaker. Those adverse events could be related to less adequate myocardial protection, but also could be associated with the surgical procedure itself. There were no clinical consequences of these events, and the echocardiographic control of the left ventricular function showed no difference between the patients from both groups. Kidney function assessed by urinary output and lung function assessed by duration of ventilation support did not differ in both groups.

The amount of heparin and protamine used showed no difference in the two groups. Postoperation, after administration of protamine, both groups still had prolonged ACT values and significantly lower plasma fibrinogen concentration when compared to the "baseline" values, but Group 1 −32°C also had significantly longer APTT in comparison to Group 2 −28°C. Mean blood loss was least in the moderate hypothermia group, but the difference did not reach significance. Hematologic data suggested increased fibrinolitic potential in the mild hypothermia group (15).

CONCLUSIONS

Our study documented no difference in organ preservation depending on type of hypothermia, mild or moderate, used during the reconstruction of VSD in pediatric patients. Adequacy of CPB was not impaired by the chosen temperatures. There was no difference in technical complexity of the operation. Moreover, the clinical outcome of the patients did not depend on the type of hypothermia. There were suggestions of more activation of fibrinolitic potential in the 32°C group.

REFERENCES

1. Cameron DE, and Gardner TJ. Principles of clinical hypothermia. Card Surg State Art Rev. 1988;2:13–25.
2. Hickely RF, and Hoar PF. Whole body oxygen consumption during low-flow hypothermic cardiopulmonary bypass. J Thorac Cardiovasc Surg. 1983;86:903–6.
3. Swain JA, McDonald TJ Jr, Balaban RS, et al. Metabolism of the heart and brain during hypothermic cardiopulmonary bypass. Ann Thorac Surg. 1991;51:105–9.
4. Moore FD, Warner KG, Assousa S, et al. The effects of complement activation during cardiopulmonary bypass: Attenuation by hypothermia, heparin, and hemodilution. Ann Surg. 1988;208:95–103.
5. Utley JR, Wachtel C, Cain RB, et al. Effects of hypothermia, hemodilution, and pump oxygenation on organ water conyent, blood flow, oxygen delivery, and renal function. Ann Thorac Surg. 1981;31:121–33.
6. Ohata T, Sawa Y, Kadoba K, et al. Effect of cardiopulmonary bypass under tepid temperature on inflammatory reactions. Ann Thorac Surg. 1997;64:124–8.
7. Lichtenstain SV, Ashe KA, El-Dalati H, et al. Warm heart surgery. J Thorac Cardiovasc Surg. 1991;101:269–74.
8. Oomen JA, Wijers M, Bos E, Schuurbier J. Automated bookkeeping in the operating room. Thoraxcentre J. 1994; 6:23–6.
9. Burgerhout A. Electronic hearts controlling lung machines. Thoraxcentre J. 1993;5:44–8.
10. Bol-Raap G, Bogers AJJC, Boersma H, et al. Temporary tricuspid valva detachment in closure of congenital ventricular septal defect. Eur J Cardiothorac Surg. 1994;8: 145–8.
11. Zwischenberger JB, Kirsch MM, Dechter RE. Suppression of shivering decreases oxygen consumption and improves hemodynamic stability during postoperative rewarming. Ann Thorac Surg. 1987;43:428–32.
12. Matsuda H, Sasako Y, Susune N, at al. Determination of optimal perfusion flow rate for deep hypothermia cardiopulmonary bypass in the adults based on distribution of blood flow and oxygen consumption. J Thorac Cardiovasc Surg. 1992;103:541–8.
13. Dale J, Lilleasson P, Erikssen J. Hemostasis after open-heart surgery with extreme or moderate hemodilution. Euro Surg Res. 1987;19:339–42.
14. Mora CT, Henson MB, Weintraub WS, et al. The effect of temperature management during cardiopulmonary bypass on neurologic and neuropsychologic outcome in patients undergoing coronary revascularization. J Thorac Cardiovasc Surg. 1996;112:514–22.
15. Engelman RM, Pleet AB, Rousou JA, et al. What is the best perfusion temperature for coronary revascularization? J Thorac Cardiovasc Surg. 1996;112:1162–3.