Jpn Circ J 2000; **64:** 436–444

Influence of Cardiopulmonary Bypass Temperature on Circulatory Pathophysiology and Clinical Outcomes

Kazuhiro Hashimoto, MD; Tatsuumi Sasaki, MD; Takashi Hachiya, MD;
Katsuhisa Onoguchi, MD; Hiromitsu Takakura, MD;
Motohiro Oshiumi, MD; Sigeyuki Takeuchi, MD

This study was designed to investigate the effects of cardiopulmonary bypass (CPB) perfusion temperature. Forty-four patients who had undergone elective coronary bypass surgery were randomly divided into 2 groups (22 patients each) according to their perfusion temperature (N group=36°C; L group=30°C). The concentrations of endogenous catecholamines, complements, elastase, serotonin, arachidonic acid metabolites and endothelin underwent various changes throughout the CPB but did not exhibit any statistical differences in either group. None of the substances measured correlated with systemic vascular resistance at any time. The temperature of the perfusion appears to be a major determinant of vascular tone. The postoperative PO_2 was better, and postoperative pulmonary vascular resistance lower in the N group ($p<0.05$), most likely because of a much larger water balance during hypothermic CPB ($p<0.01$). The postoperative blood loss was statistically less in the N group ($p<0.05$). Although apparent brain damage, evidenced by the leakage of creatine kinase-BB, was not seen, the jugular bulb venous hemoglobin saturation levels (<50% in 27% of the N group, $p<0.05$) and higher lactate levels suggested that normothermic perfusion was relatively disadvantageous. It is concluded that normothermic CPB was relatively safe and advantageous with regard to hemostasis and pulmonary function. (*Jpn Circ J* 2000; **64:** 436–444)

Key Words: Cardiopulmonary bypass; Normothermia; Perfusion; Vasoactive mediator

Cardiac surgery involving a cardiopulmonary bypass (CPB) results in alterations of hemodynamics, microcirculation and metabolism as well as systemic inflammatory responses because of the changes in circulatory physiology and the activation of blood components[1]. Vital organs can be injured, so sufficient O_2 delivery to meet organ demand is an important factor during CPB. Systemic hypothermia during CPB has been regarded as essential for some degree of organ protection, particularly of the brain, but there are some disadvantages of hypothermic CPB[1]. Recently, the use of normothermic CPB has been reported to confer advantages over conventional hypothermic CPB, including preservation of the coagulation process and a reduction in bleeding, hemodynamic stability and a shorter period of intubation[2–7]. There is interest in the effects of perfusion temperature on circulatory physiology and the systemic inflammatory responses during CPB, which if they exist, may have an important clinical influence on the patients' outcome.

The present study was designed to investigate the effects of CPB perfusion temperature on various vasoactive mediators, inflammatory responses and the endothelium, as well as its potential to alter clinical outcomes. We also hoped to clarify the influence of CPB temperature on cerebral circulation in regard to preventing brain damage and the mechanisms that lead to different clinical outcomes.

(Received November 8, 1999; revised manuscript received February 7, 2000; accepted February 21, 2000)
Department of Cardiovascular Surgery, Saitama Cardiovascular and Respiratory Center, Saitama, Japan
Mailing address: Kazuhiro Hashimoto, MD, Saitama Cardiovascular and Respiratory Center, 1696 Itai, Konan-machi, Osato-gun, Saitama-ken 360-0105, Japan

Methods

Forty-four patients undergoing elective coronary bypass surgery were selected after obtaining the approval of the ethics committee of our institution and getting written informed consent from the patients. The patients were randomly selected and divided into 2 groups (22 patients in each group) according to their CPB perfusion temperature: either normothermic (36°C) or hypothermic (30°C) perfusion. Two surgeons performed the operations and they were not informed of the perfusion temperature.

Anesthesia was induced by intravenous injection of 30 μg/kg of fentanyl and 0.2 mg/kg of vecuronium, and the trachea was then intubated. After induction of anesthesia, a pulmonary artery catheter (Vigilance Swan-Ganz CCO Thermodilution Catheter; Baxter Healthcare Corp, Irvine, CA, USA) was inserted through the right internal jugular vein. The jugular bulb venous hemoglobin saturation ($SjVO_2$) was monitored with a 4F catheter inserted retrogradely into the right jugular bulbi, with the position of the catheter verified radiographically. The CPB was performed with a nonpulsatile flow at the highest possible rate, approximately 2.8–3.0 $L \cdot min^{-1} \cdot m^{-2}$, irrespective of the perfusion temperature. The patients were monitored by alpha-stat control of the arterial blood gases using a membrane oxygenator with hollow polypropylene fibers and polyvinyl chloride tubing in both groups. Prime volumes were the same in both groups and consisted of 1600 ml of electrolyte solution, 50 ml of 7% sodium bicarbonate, and 20 g of mannitol. The diuretic (furosemide 20 mg) were added to the prime and any additional use of diuretics was prohibited during CPB. The perfusion pressures were maintained at round 60 mmHg in the both

groups. Phenylephrine and nitroglycerin were used for pressure control during the CPB. Anticoagulation monitoring during the CPB was performed by Kaolin activated clotting time (ACT) tests and, more accurately, real-time heparin measurements using Hepcon (a whole blood hemostasis system; Medtronic Hemotec, Englewood Co, USA)[9,10] A heparin dose–response assay was used to automatically measure the ACT and determine the initial and additional doses of heparin required to maintain the ACT at 480 s, which we considered to be a safe level for CPB. Appropriate levels of whole blood heparin (ranging on average from 5.0 to 3.0 IU/ml) were meticulously maintained throughout the CPB. At the termination of the CPB, the appropriate amount of protamine required to neutralize the heparin was determined by titration of protamine to heparin[9,10]

The same components of cold blood cardioplegic solution were delivered ante- and retrogradely, but the temperature of the cardioplegic solution reaching the aortic root was different, because the cooling capacity of the cardioplegic delivery system was flow-limited. Myocardial temperature was measured after the termination of initial cardioplegic administration. Retrograde cardioplegia was performed twice; once immediately after the initial antegrade delivery, and once as part of the terminal warm cardioplegia immediately before the initiation of antegrade terminal warm cardioplegia. After the completion of each graft anastomosis, antegrade cardioplegia was performed with selective delivery to the grafts. The pericardial well was soaked with cold saline (without ice) for topical cooling. Blood transfusion and platelet infusions were not performed during the CPB. All anastomoses in the coronary bypass surgery, proximal and distal, were performed during single aortic clamping.

Some patients were excluded from this series because of one of the following reasons: (1) emergency case, (2) a history of previous cardiac operation, (3) coexistent valvular heart disease, (4) renal failure, or (5) apparent cerebrovascular or lung disease.

Blood samples were taken 6 times during the operation: (1) after the administration of the anesthetic (baseline data), (2) 10 min after the initiation of the CPB, (3) 30 min after aortic clamping, (4) 60 min after aortic clamping, (5) at the end of the CPB, and (6) on admission to the intensive care unit (ICU). All the blood samples were immediately centrifuged, and the plasma was stored at −70°C for laboratory assay at Sumitomo Bio-Science, Omiya, Japan.

Measurements

Alteration of Vasoactive Mediators Blood samples were collected in tubes containing ethylenediaminetetraacetic acid (EDTA) disodium. Serum levels of the major vasoactive substances (catecholamines (norepinephrine, epinephrine, dopamine), antiduretic hormone and angiotensin II) were measured. Serum catecholamine levels were measured using high-performance liquid chromatography; angiotensin II and antiduretic hormone levels were measured using double antibody radio-immunoassays.

Granulocyte Activation

Granulocyte Elastase and Protease Inhibitor Blood samples to measure elastase were collected in empty tubes. The enzyme-linked immunoassay demonstrated that the plasma elastase formed a complex with α_1-protease inhibitor. The measured level of elastase therefore expressed the value of inactivated elastase. The α_1-protease inhibitor, which is the major elastase inhibitor in the serum, was measured using a double antibody radio-immunoassay.

Platelet Activation and Endothelial Function

Arachidonic Acid Metabolites Blood samples to measure arachidonic acid metabolites were collected in tubes containing indomethacin and EDTA disodium. Since both prostaglandin I_2 and thromboxane A_2 are promptly metabolized, their stable metabolites, prostaglandin $F_{1\alpha}$ and thromboxane B_2, were measured using double antibody radio-immunoassays.

Serotonin Blood samples were collected in tubes containing EDTA disodium. Serotonin levels were measured using high-performance liquid chromatography.

Endothelin Each blood sample was collected in a tube that contained EDTA dipotassium. Endothelin was measured using a double antibody radio-immunoassay.

Complements

Blood samples to measure complements were collected in empty tubes. Complements C3 and C5 were measured using direct radio-immunoassays.

Routine Hematological and Biochemical Analyses

Blood cell counts were analysed preoperatively and immediately after termination of the CPB. The following measurements were made both pre- and postoperatively: aspartate aminotransferase (GOT), alanine aminotransferase (GPT), lactate dehydrogenase (LDH), creatine kinase (CK), CK-MB, blood urea nitrogen (BUN), and creatinine. These measurements were performed with fully automated hematological (Coulter STKS, Beckman counter, Tokyo) and biochemical analysers (JTA-HR2200 Clinalyzer, Nihon Denshi, Tokyo, Japan).

Evaluation of Cerebral Circulation

Blood samples were taken from the jugular bulb during the cardiac surgery and used to measure $SjVO_2$, lactate and CK-BB levels.

Blood Gas

The PO_2 at 1.0 of the fractional concentration of inspired oxygen was measured after delivery of the anesthetic and immediately after admission to the ICU. The tidal volume (10 ml × body weight, kg) and positive end-expiratory pressure (PEEP) (3 cm H_2O) were consistent in all patients.

Cardiac and Hemodynamic Evaluation

To evaluate the degree of cardiac damage sustained during aortic clamping, the level of myocardial leaking enzyme (CK-MB) was measured postoperatively (ICU admission, 6 h and 1st postoperative day) and the maximum values of both groups were compared.

Arterial, pulmonary arterial, pulmonary capillary wedge, and central venous pressures were measured using pressure transducers connected directly to the radial artery and a Swan-Ganz catheter. The cardiac output was determined using the thermodilution technique by a Swan-Ganz catheter. Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were calculated using a standard formula.

Clinical Outcome

Blood Loss and Blood Transfusion Postoperative medi-

astinal drainage was monitored and measured for the first 24 h after surgery. Units of blood transfusion for this time period were also recorded and the results of both groups were compared.

Urine Volume and Water Balance During CPB The urine volume and water balance during the CPB were calculated after the termination of the CPB.

Adverse Events

The occurrence of perioperative myocardial infarction (a new q wave, CK-MB more than 80 IU/L), cerebral infarction and cerebral hemorrhage was noted.

Statistical Analysis

All data were expressed as the mean ± standard deviation. Analysis of variance for repeated measurements was used to test for significance between and within groups. Post hoc data were analysed by paired or unpaired t tests when appropriate, with Bonferroni corrections for multiple comparison. The frequency was compared in the 2 groups by means of the standard chi-square test. The coefficient of correlation between 2 variables was calculated by Spearman's rank-difference technique. Differences were considered to be significant when the p value was equal to or less than 0.05.

Table 1 Patient Data

	CPB temperature	
	30°C	36°C
Age (years)	66±8	64±9
Sex (M/F)	6/17	7/15
BW (kg)	60±10	62±9
CPB time (min)	133±27	117±33
Aortic clamp time (min)	90±21	88±29
No. of grafts	2.8±0.7	2.7±0.8
LITA use	22/22	21/22

No significance between 2 groups. BW, bodyweight; CPB, cardiopulmonary bypass.

Results

The baseline characteristics of the study participants are listed in Table 1. The groups were matched with regard to all preoperative demographic and operative variables except for the CPB perfusion temperature. However, the duration of the CPB was slightly longer in the hypothermic group ($p<0.1$). The initial dose of heparin was 21,300± 5,700 IU for the normothermic group and 20,500±6,200 IU for the hypothermic group. Whole blood heparin levels were consistent in all patients, with an initial value of around 7.5 IU/ml and subsequent values ranging between 3.0 and 4.5 IU/ml throughout the CPB. Serum heparin was completely reversed after the termination of the CPB with a dose of protamine that was calculated by the Hepcon. The myocardial temperatures measured after the administration of cardioplegia were 11±2°C in the hypothermic group and 18±2°C in the normothermic group. Despite rewarming to a rectal temperature of 37°C before terminating the CPB in the hypothermic group, the rectal temperature upon ICU

Table 2 Trends of the Vasoactive Mediators

		Pre	CPB 10 min	Ao 30 min	Ao 60 min	CPB off	ICU
Epinephrine (ng/ml)	36°C	0.03±0.02	0.2±0.19**	0.23±0.25**	0.24±0.25**	0.09±0.08**#	0.1±0.12**#
	30°C	0.03±0.03	0.18±0.12**	0.18±0.11**	0.16±0.13**	0.05±0.03**	0.05±0.03**
Norepinephrine (ng/ml)	36°C	0.28±0.18	0.92±0.96**	1.51±1.62**	1.73±1.64**	1.53±1.73**	2.64±2.62**
	30°C	0.27±0.21	0.6±0.38**	1.07±1.88*	1.07±1.61*	1.08±1.78*	2.09±1.99**
Dopamine (ng/ml)	36°C	1.61±3.03	4.88±6.6*	2.73±3.91	3.13±5.89	20.7±34.8*	147.3±105.4**
	30°C	1.49±1.78	3.54±5.17	2.37±3.9	2.88±4.7	27.3±33.7**	140.5±62.1**
Angiotensin II (pg/ml)	36°C	85.4±55.4	80.8±43.4	154.9±81.3**	149.2±109.6*	125.6±88.4*	89.2±63.9
	30°C	79.2±76.6	64.9±49.2	124.7±120.5*	134.8±146.4*	139.1±159.9	95.1±62.6
ADH (pg/ml)	36°C	1.99±1.06	3.63±0.93*	3.87±0.73**	4.81±1.93**	5.53±2.15**	6.9±5.19
	30°C	1.83±1.16	5.68±1.94**	5.33±1.49**	5.53±1.9**	5.76±2.46**	6.26±4.02**

*$p<0.05$, **$p<0.01$ vs preoperative data. #$p<0.05$, ##$p<0.01$ vs 30°C.*

Table 3 Blood, Endothelium and Complement Activation

		Pre	CPB 10 min	Ao 30 min	Ao 60 min	CPB off	ICU
Elastase (ng/dl)	36°C	109.1±16.1	124.8±50.7	128.7±59.4	132.3±57.7	149.8±76.4*	154.9±79.6*
	30°C	110.2±19	122.1±64.4	125.1±78.8	125.5±75.1	129.5±69.1	153.3±82.8*
Protease inhibitor (ng/dl)	36°C	1.96±1.3	2.57±2.6	5.86±5.15**	6.64±6.29**	6.0±5.95*	4.39±2.68**
	30°C	1.97±1.46	2.86±3.07	4.28±4.09*	6.33±5.0**	6.0±3.44**	3.97±2.18**
Thormboxane B_2 (pg/ml)	36°C	51±39	171±159**	211±215**	221±221**	227±179**	63±81
	30°C	54±41	142±95**	194±109**	210±193**	238±179**	68±74
Prostaglandin $F_{1\alpha}$ (pg/ml)	36°C	161±36	302±42**	334±38**	364±58**	402±65**	301±65**
	30°C	153±33	286±46**	323±39**	367±51**	387±59**	294±61**
Serotonin (μg/dl)	36°C	9.1±4.6	21.4±11.3**	14.4±10.5**	12.9±7.2*	11.0±4.6*	5.7±2.8**
	30°C	9.3±3.7	22.0±9.2**	14.5±7.4**	11.5±4.6	10.9±2.7	6.0±2.7**
Endothelin (pg/ml)	36°C	6.7±3.8	8.6±3.1**	9.3±2.5**	9.8±2.8**	10.4±3.0**	11.6±3.9**
	30°C	6.3±2.0	8.0±2.9**	9.1±3.1**	9.6±3.0**	10.6±3.6**	11.6±3.8**
C3 (mg/dl)	36°C	70±10	33±4**	36±5**	37±5**	37±5**	40±4**
	30°C	69±11	32±5**	34±5**	35±5**	35±4**	39±5**
C5 (mg/dl)	36°C	12±3	5.5±1.1**	6.5±1.3**	6.6±1.5**	6.6±1.6**	7.3±1.6**
	30°C	11.9±1.5	5.7±0.9**	6.1±1.2**	6.4±1.3**	6.4±1.2**	7.5±1.3**

*$p<0.05$, **$p<0.01$ vs preoperative data. No significance between 2 groups.*

Table 4 Hematological and Biochemical Analysis

		Pre	ICU (pump-off)	Max
Hb (g/dl)	36°C	12.8±1.7	12±1.9	
	30°C	13.1±1.5	11.8±1.2	
Ht (%)	36°C	42.3±3.6	38.7±4.2	
	30°C	44.1±3.4	36.4±3.0	
WBC ($\times10^3/\mu l$)	36°C	6.76±1.79	(15.2±4.93)	
	30°C	7.26±1.79	(13.8±3.47)	
Platelet ($\times10^3/\mu l$)	36°C	17.2±56.3	(8.4±3.1)	
	30°C	16.8±41.8	(8.1±2.3)	
GOT (IU/L)	36°C	25±14	63±48	89±62
	30°C	26±11	67±26	115±75
GPT (IU/L)	36°C	24±15	24±23	28±25
	30°C	25±15	23±17	33±19
LDH (IU/L)	36°C	319±67	727±292	838±365
	30°C	337±95	734±241	1011±436
CK-MB (IU/L)	36°C	16±10	41±14##	52±23##
	30°C	16±10	59±17	71±17
CK (IU/L)	36°C	72±34	425±194##	1250±786#
	30°C	74±31	590±200	1836±893
BUN (mg/dl)	36°C	18±6	15±5	23±10
	30°C	17±4	15±4	21±4
Creatinine (mg/dl)	36°C	0.9±0.4	1.0±0.4	1.2±0.4
	30°C	0.9±0.1	1.0±0.3	1.2±0.3

#p<0.05 vs 30°C, ##p<0.01 vs 30°C. pump-off, at the termination of cardiopulmonary bypass.

admission was significantly lower in the hypothermic group (35.8±0.3°C vs 36.3±0.2°C in the normothermic group, p<0.01). There were no operative deaths in this series.

Vasoactive Mediators (Table 2)

The significance of the change in levels, as compared to baseline values, of vasoactive substances, such as epinephrine, norepinephrine, dopamine, angiotensin II and antiduretic hormone, are shown in Table 2. Only epinephrine levels in the normothermic group at the termination of the CPB and upon ICU admission were statistically higher than corresponding levels in the hypothermic group (p<0.05). The other mediators exhibited similar trends and values in both groups throughout the study period. The levels of catecholamines increased continuously throughout the period of the CPB, began to decrease soon after the termination of the CPB and had returned to the baseline values by the time of admission to the ICU. An elevation of dopamine immediately after the termination of the CPB was the only exception, and this was caused by the administration of exogenous dopamine ($6.7\pm2.5\,\mu g\cdot min^{-1}\cdot kg^{-1}$). The levels of angiotensin II were diluted at the time of CPB initiation, but started to increase soon after and remained at elevated levels throughout the CPB, returning to the baseline values upon admission to the ICU. No differences in the trends and levels were seen between the 2 groups. The level of antiduretic hormone gradually increased throughout the CPB until the time of admission to the ICU. Again no differences were observed between the 2 groups.

Granulocyte Activation (Table 3)

Granulocyte Elastase and Protease Inhibitor Elastase levels increased gradually throughout the period of measurement. In the normothermic group, the levels at the time of CPB termination and ICU admission were significantly higher than the baseline value. Only the level at the time of ICU admission was higher than the baseline value in the hypothermic group. However, the amount of elastase released from the activated granulocytes was the same in both groups. The level of α_1-protease inhibitor also increased gradually throughout the period of measurement, without any variation between groups.

Platelet Activation and Endothelial Function (Table 3)

Arachidonic Acid Metabolites In both groups, the levels of thromboxane B_2 increased immediately after the initiation of the CPB and continued to increase until the termination of the CPB. By the time of ICU admission, the level had returned to a value that was close to the baseline. The level of prostaglandin $F_{1\alpha}$ during the CPB demonstrated a similar trend, but at ICU admission, the level was still statistically higher than the baseline value. No differences were observed between the 2 groups throughout the period.

Serotonin An immediate increase of serotonin levels was observed after the initiation of the CPB in both groups. The levels subsequently decreased slightly, but remained at elevated levels until the termination of the CPB. No differences were observed between the hypothermic and the normothermic groups.

Endothelin The concentration of endothelin increased after the initiation of the CPB and continued to gradually increase until the time of ICU admission. No differences in either the trend or the values were observed between the 2 groups.

Complements (Table 3)

The levels of complements decreased drastically after the initiation of the CPB because of hemodilution and consumption, and although the latter was small in both groups, the complement levels did not return to the baseline values in either group.

Routine Hematological and Biochemical Analysis (Table 4)

The change between the pre- and postoperative blood cell counts was the same in both the normothermic and the

Table 5 Cerebral Circulation

		Pre	CPB 10 min	CPB 30 min	CPB 60 min	CPB Warming	CPB off	ICU
$SjVO_2$ (%)	36°C	62±9	63±7	56±7*##	56±8*		64±6	62±7
	30°C	63±9	61±7	64±7	61±7	62±8	68±9	67±7
Lactate (mg/dl)	36°C	9.9±2.8	27.1±4.9*##	30.4±10.6**	32.7±14.3**		40±15.2**	33.9±12.8**
	30°C	8.6±1.5	21.7±4.1**	26.1±7.5**	29.6±7.6**	34.1±10.7	37.5±11.7**	39.7±10.1**
CK-BB (U/L)	36°C	0.8±0.4	1.2±0.3*	2.6±1.0**	3.3±0.8**		5.8±0.8**	5.6±0.8**
	30°C	0.9±0.2	1.5±0.5**	2.8±0.7**	3.9±1.0**	5.2±1.3**	6.0±0.7**	5.6±1.4**

*$p<0.05$, **$p<0.01$ vs preoperative data. #$p<0.05$, ##$p<0.01$ vs 30°C.

Table 6 Systemic Vascular Resistance and Cardiac Index

	Minimum	CPB 10 min	Ao 30 min	Ao 60 min	CPB off	ICU	Phenylephrine	CI at ICU
Normothermia (36°C)	779±215#	1173±374	1526±363	1593±372	1879±336	1738±479#	2.4±1.9##	2.9±0.8
Hypothermia (30°C)	978±274	1270±449	1396±330	1676±455	1916±331	2171±720	0.6±0.2	2.7±0.7

#$p<0.05$, ##$p<0.01$ vs 30°C. SVR, dyne·s·cm^{-5}; Phenylephrine, mg; CI, L/m^2.

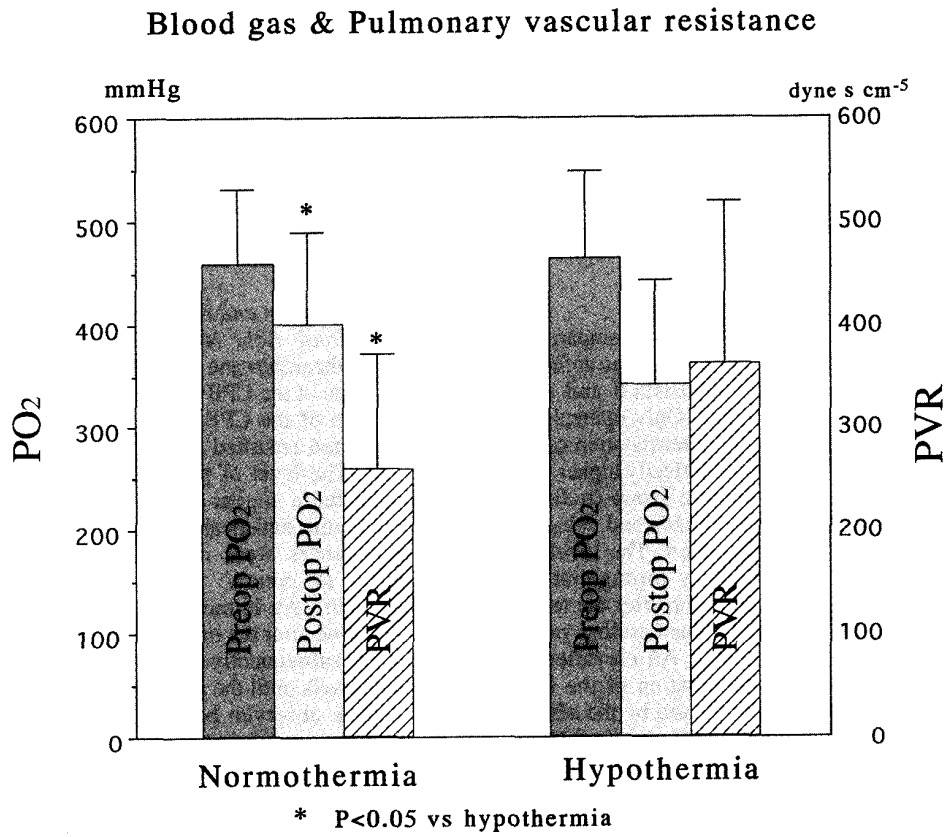

Fig 1. Significant differences in postoperative PO_2 and PVR levels were observed upon admission to the ICU between the 2 groups.

hypothermic groups.

The postoperative levels of GOT, GPT and LDH were the same in both groups, but the values of CK and CK-MB were higher in the hypothermic group ($p<0.01$). Serum creatinine and blood urea nitrogen levels increased one day after surgery, but the magnitude of the increase was similar in both groups.

Evaluation of Cerebral Circulation (Table 5)

The levels of $SjVO_2$, lactate and CK-BB in the jugular bulbi are shown, along with all significant changes. The hematocrit (influential to $SjVO_2$ values) in the 2 groups did not different during the CPB. The $SjVO_2$ level in the normothermic group decreased after the onset of CPB and remained decreased until the termination of the CPB, upon which the level returned to its baseline value. The reductions at 30 and 60 min of CPB were statistically significant to the baseline values ($p<0.05$). On the other hand, the $SjVO_2$ level in the hypothermic group remained at its baseline value throughout the duration of the CPB. Thirty

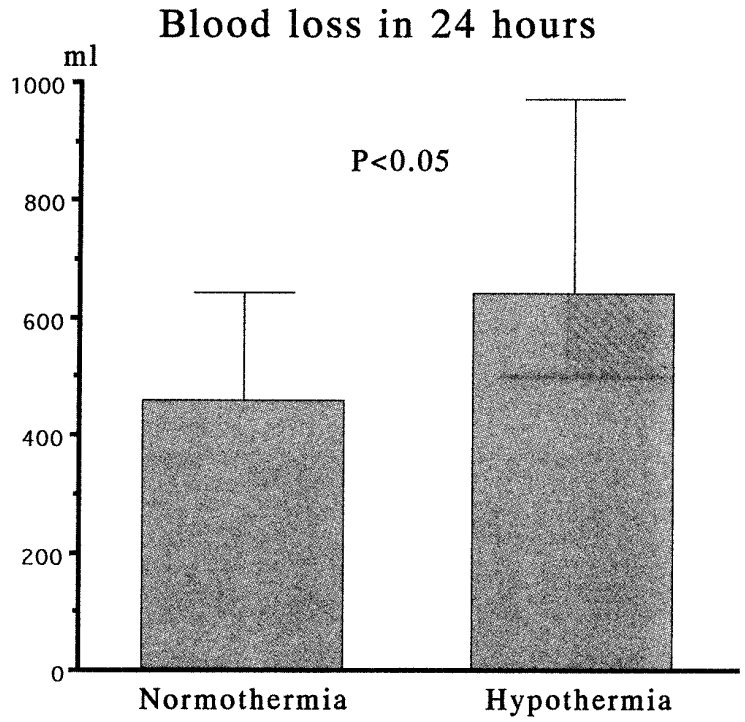

Fig 2. The volume of mediastinal drainage after surgery was significantly lower in the normothermic group.

minutes after the initiation of the CPB, the $SjVO_2$ level in the normothermic group was significantly lower than that in the hypothermic group ($p<0.01$), but no other statistical differences were observed. The $SjVO_2$ level fell to less than 50% (considered a critical level) in 6 cases (27%) in the normothermic group, usually during the early period of the CPB. Such a situation occurred only once (during the warming period) in the hypothermic group ($p<0.05$).

The levels of lactate in the jugular bulb was elevated throughout the CPB in both groups ($p<0.01$–0.05) and reached a somewhat higher level in the normothermic group, which was only significant right after the initiation of the CPB ($p<0.05$).

The level of CK-BB in the jugular bulb was nearly the same throughout the CPB and upon ICU admission. The levels were statistically higher than the baseline values ($p<0.05$–0.01), but no differences between the groups were observed throughout the study period.

Blood Gas (Fig 1)

The baseline data for the PO_2 at 100% oxygen inspiration was identical in both groups (458±72 mmHg in the normothermic group and 463±85 mmHg in the hypothermic group). However, a significant difference in postoperative PO_2 levels at 100% oxygen inspiration was observed upon admission to the ICU: 400±89 mmHg in the normothermic group and 341±101 mmHg in the hypothermic group ($p<0.05$).

Cardiac and Hemodynamic Evaluation (Table 6)

The SVR at initiation of CPB was significantly smaller in the normothermic group than in the hypothermic group ($p<0.05$). Phenylephrine was administered to maintain a proper perfusion pressure, so the SVR in the normothermic group was kept at the same level as the hypothermic group throughout the CPB. Nitroglycerin was necessary only in the hypothermic group, at a dose of 1.8±1.0 mg. The SVR in the hypothermic group increased upon admission to the ICU, resulting in a statistically significant difference ($p<0.05$). The amount of phenylephrine that was used in the normothermic group was significantly larger ($p<0.01$). No correlation was observed, either during the CPB or upon ICU admission, between the levels of vasoactive mediators, elastase or complements and the SVR.

The PVR upon admission to the ICU was significantly different in the 2 groups (259±112 dyne·s·cm^{-5} in the normothermic group and 362±157 dyne·s·cm^{-5} in the hypothermic groups, $p<0.05$, Fig 1). None of the vasoactive mediators, elastase or complements showed any correlation with the PVR at the time of ICU admission.

The cardiac index measured at the time of ICU admission was the same in both groups (Table 6).

Clinical Outcomes

Blood Loss (Fig 2) and Blood Transfusion The volume of mediastinal drainage collected 24 h after surgery was significantly lower in the normothermic group than in the hypothermic group (459±185 and 641±331 ml, respectively, $p<0.05$). The amount of blood transfusion required was 0.8±0.8 U in the normothermic group and 1.1±0.7 U in the hypothermic group, which was not significantly different.

Urine Volume and Water Balance During CPB (Fig 3) The volume of urine collected during the CPB was not statistically different between the 2 groups: 486±342 ml in the normothermic group and 611±400 ml in the hypothermic group. The serum antiduretic hormone concentrations were also the same in both groups. However, the water balance at the time of the CPB termination was statistically less ($p<0.01$) in the normothermic group (–473±756 ml) than in the hypothermic group (+526±902 ml).

Adverse Events

Postoperative cerebral infarction or hemorrhage did not occur in either of the 2 groups. Perioperative myocardial

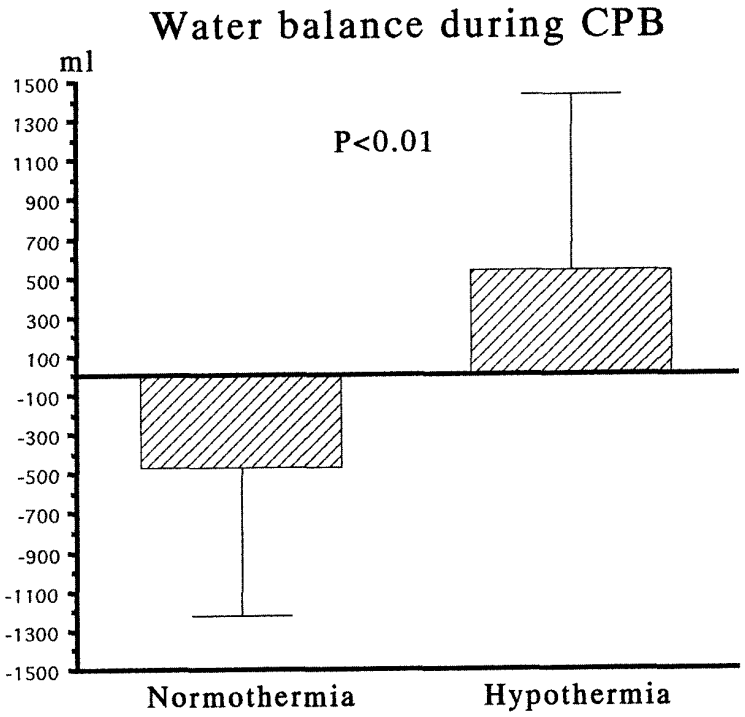

Fig 3. The water balance during CPB was statistically less in the normothermic group.

infarction was also not observed in this series.

Consideration

The use of moderate systemic hypothermia during open heart surgery has been believed to be the most important component in the protection of vital organs via the reduction of metabolic and oxygen requirements. However, recent advances in CPB instruments and devices (oxygenators and efficient pumps) have altered the importance of reduced body temperature and reports on the safety of normothermic CPB has encouraged its application[2-7] The body's response to foreign materials and to the specific circulation pattern that occurs during hypothermic CPB is well documented[1,8-11] Neutrophils in the complement cascade are activated, and platelet aggregation is accelerated. Moreover, CPB triggers the production and release of various vasoactive mediators. However, questions remain as to whether similar responses occur during normothermic perfusion and whether the alterations, if they exist, are advantageous to the patient.

The important findings of the present study are summarized as follows.

(1) The concentrations of endogenous catecholamines (epinephrine, norepinephrine and dopamine) increased during the CPB, but were not influenced by the perfusion temperature.

(2) The levels of complements, elastase, serotonin and thromboxane B_2 underwent various changes throughout the CPB, but did not show any statistical difference between 2 groups, suggesting that the activation of complements and blood components are induced to the same degree, regardless of the perfusion temperatures.

(3) The levels of endothelium-derived substances (endothelin and prostaglandin $F_{1\alpha}$) were similar in both groups, suggesting that the effects of the CPB on the endothelial vasoactive function were not influenced by the perfusion temperature.

(4) During the CPB, the SVR was significantly lower in the normothermic group. None of the vasoactive mediators measured in this study correlated with the SVR at any time during or after the CPB. Although the urine volume collected during the CPB was similar in both groups, the water balance during the CPB was statistically less in the normothermic group.

(5) The postoperative PO_2 was better in the normothermic group and the pulmonary vascular resistance upon ICU admission was statistically higher in the hypothermic group.

(6) Postoperative blood loss within 24 h of surgery was statistically less in the normothermic group.

(7) Apparent brain damage, evidenced by clinical neurological deficits or the severe levels of CK-BB leakage, was not seen in the normothermic group. However, $SjVO_2$ and lactate levels suggested that hypothermic perfusion was safer in regard to protecting the brain.

The decrease in the SVR during normothermic CPB has been well-documented[2,8,9] and appears to be more common in patients with better cardiac function and in younger patients without peripheral vascular disease[12] We found that the concentrations of endogenous catecholamines and other vasoactive mediators circulating in the body were equal in both groups. Because plasma norepinephrine reflects sympathetic nervous activity, sympathetic activity (as determined by changes in plasma norepinephrine concentration) was not significantly influenced by the temperature in this study. Plasma epinephrine concentrations, indicating adrenal medullary activity, were also not influenced. Other vasoactive mediators were also circulating at equal levels: (1) prostaglandin I_2: released from the endothelium and the most potent inhibitor of platelet aggregation and vasodilatation; (2) thromboxane A_2: released from platelets, activating platelet aggregation and vasoconstriction; (3) serotonin: released from activated platelets, causing an endothelium-dependent relaxation, but if the

endothelium is dysfunctional or injured, monoamines exert a direct constrictive effect on vascular smooth muscle; and (4) endothelin: synthesized and released as a vasoconstrictor peptide by endothelial cells. None of the substances measured in this study correlated with the SVR at any time, either during or after the CPB. Other vasoactive substances (endotoxin, kinins) and hormones, such as renin, atrial natriuretic peptide, prolactin and thyroxine, were not examined, but no differences were found in previous reports[13–15] With these points in mind, the temperature of the perfusion appears to be a major determinant of vascular tone. The decreased vascular tone prompted the administration of phenylephrine in order to maintain normal vascular tone during the normothermic CPB. During hypothermic CPB, cold perfusion induces the shutdown of various vascular beds and the higher blood viscosity may also result in a higher SVR. The increase in the SVR that was observed in the present hypothermic group upon admittance to the ICU was probably a result of the drop in body temperature that occurred after incomplete CPB rewarming.

The postoperative PVR was higher and the postoperative PO_2 lower in the hypothermic group. Lehot et al reported the same tendency for PO_2 and PVR levels, although the differences were not significant in their series[14] As our previous investigation[11] and others[8–10] have suggested, pulmonary damage during CPB is mainly caused by the activation of neutrophils (endothelial adhesion, protease and free radicals) and complements. In addition, elevated thromboxane A_2 and endothelin levels may result in pulmonary vascular constriction[11] In the present study the changes in the aforementioned factors showed no significant differences between the 2 groups either during CPB or after admission to the ICU when the postoperative PVR and PO_2 were measured. Recent reports have suggested that levels of cytokines (tumor necrosis factor, interleukin (IL)-6 and IL-8), which are of current interests and triggers of inflammatory reaction in the body, increase during CPB. However, the increment was not different between the normothermic and hypothermic groups[7,15] Thus, inflammatory damage to the lungs during the CPB was probably not influenced by the perfusion temperature. The slightly longer CPB time in the hypothermic group as a result of the rewarming period and the imperfection of the rewarming (evidenced by the low rectal temperature upon ICU admission) might have resulted in deterioration of the pulmonary vascular condition and gas exchange capability. The difference in the water balance observed during the CPB might also have had an effect. The shift of fluid occurred mainly during the rewarming phase of the hypothermic perfusion and resulted in a positive water balance. The lower postoperative fluid requirements accompanying normothermic perfusion, as suggested by Massimino et al[16] may be due to fewer capillary leaks. In addition, Singh et al have reported that normothermic perfusion allows the right ventricle to be better preserved, which is beneficial to pulmonary circulation[2] The effects of perfusion temperature on pulmonary gas exchange were also evaluated by Birdi et al[17] They concluded that the perfusion temperature did not influence the alveolar-arterial oxygen pressure gradient. The differences between their study and ours are probably related to the shorter period of CPB and complete rewarming of the patients in their series.

Previous investigations regarding hemostasis after normothermic CPB indicated a reduction in blood loss and the number of blood transfusions required[5–7] In the present study, heparin levels were properly and accurately controlled by real-time measurements of whole blood heparin levels to eliminate the influence of improper management of heparin concentration. A heparin/protamine titration method was used to neutralize serum heparin accurately and completely[8,9] Our strict protocol for evaluation of hemostasis produced results that suggest normothermic perfusion is more advantageous than hypothermic perfusion. Although the effects of perfusion temperature on coagulation factors were not investigated, the preservation of coagulation factors is believed to be a major reason for these advantages. Boldt et al have demonstrated that hypothermic perfusion results in more pronounced alterations of platelet aggregation and endothelial-related coagulation (eg, the thrombomodulin/protein C/protein S system) than normothermic CPB[5]

Several reports have been made on the hemodynamic stability after normothermic CPB and these reports seem to indicate that lower doses of inotropic drugs and a better cardiac index with low vascular resistance are associated with normothermic perfusion[2,3,6,7] Our institute routinely uses dopamine at the weaning of CPB, so we could not confirm that lower doses of inotropes were possible. Furthermore, the nearly identical cardiac index at the time of the ICU admission did not support the hemodynamic advantage of normothermic perfusion suggested in those reports. However, significantly high endogenous epinephrine levels at the time of CPB termination and ICU admission, and the low SVR at the time of ICU admission, suggest that the postoperative hemodynamics after normothermic CPB are more stable. In addition, the advantage of a reduction of myocardial leaking enzyme (CK-MB) was observed in the normothermic CPB. The only difference in cardioplegic protection between the 2 groups was the temperature of the cardioplegic perfusate. However, no reasonable explanation for this result was found other than the one given.

Several merits of normothermic CPB have been discussed, but the lower SVR and increased need for vasoconstrictors does carry a theoretical risk of injury to the metabolically active brain. Regional perfusion abnormalities resulting from phenylephrine use (as a vasoconstrictor) were suggested during a normothermic bypass[18] but no cerebral events were observed in either the normothermic perfusion or the hypothermic perfusion in the present study. Subclinical cerebral damage was also more or less equal in both groups, as shown by the similarly elevated levels of CK-BB. We attempted to maintain a rather high perfusion pressure (60 mmHg) and a high flow rate in the normothermic group, but the reduced $SjVO_2$ levels and the elevated lactate levels in the jugular bulb might be signs of insufficient oxygen delivery. Because transient neurologic defects are mostly observed with a jugular venous saturation level of less than 50%, the $SjVO_2$ level probably becomes clinically significant when its saturation level reaches about 50%. In the present study, $SjVO_2$ levels of less than 50% were experienced in 27% of the normothermic patients[19,20] Cook et al have also suggested that a higher level of oxygen consumption is present in the brain during a normothermic CPB and demonstrated that patients undergoing normothermic CPB were at greater risk for cerebral desaturation[21] By reducing the temperature from 37°C to 27°C, however, the cerebral metabolic rate of oxygen consumption was reduced by 64%[22] Neuropsychologic outcomes after normothermic perfusion have been

investigated by several institutes;[23–26] and, in particular, the prevalence of cognitive deficits, because these deficits should be more common and more sensitive than neurologic deficits. However, conclusions regarding the risk for postoperative cognitive deficits after normothermic CPB have not been made, because both pro and contra results have been obtained. Patients with cerebrovascular disease were excluded from these studies, so a higher risk for neurologic deficits in the excluded patients might be a concern.

Conclusions

We conclude that (1) the alteration of vasoactive mediators and the activation of blood components did not vary between the hypo- and the normothermic CPB, (2) the temperature of perfusion appeared to be a major determinant of vascular tone, (3) normothermic CPB was advantageous with regard to hemostasis and pulmonary function, and (4) normothermic perfusion is relatively safe in patients with no signs of cerebrovascular disease.

References

1. Kirklin JW, Barratt-Boyes BG: Hyothermia, circulatory arrest, and cardiopulmonary bypass. *In*: Cardiac surgery, 2nd edn. New York: Churchill Livingstone, 1993: 63–94
2. Singh AK, Feng WC, Bert AA, Rotenberg FA: Warm body, cold heart surgery. *Eur J Cardiothorac Surg* 1993; **7:** 225–230
3. Tonz M, Mihaljevic T, Pasic M, von Segesser LK, Turina M: The warm versus cold perfusion controversy: A clinical comparative study. *Eur J Cardiothorac Surg* 1993; **7:** 623–627
4. The Warm Heart Investigators: Randomized trial of normothermic versus hypothermic coronary bypass surgery. *Lancet* 1994; **343:** 559–563
5. Boldt J, Knothe C, Welters I, Dapper FL, Hempelmann G: Normothermic versus hypothermic cardiopulmonary bypass: Do changes in coagulation differ? *Ann Thorac Surg* 1996; **62:** 130–135
6. Birdi I, Regragui I, Izzat MB, Bryan AJ, Angelini GD: Influence of normothermic systemic perfusion during coronary artery bypass operations: A randomized prospective study. *J Thorac Cardiovasc Surg* 1997; **114:** 475–481
7. Tonz M, Mihaljevic T, von Segesser LK, Schmid ER, Joller-Jemelka HI, Pei P, et al: Normothermia versus hypothermia during cardiopulmonary bypass: A randomized, controlled trial. *Ann Thorac Surg* 1995; **59:** 137–143
8. Chenoweth DE, Cooper SW, Hugli TE, Stewart RW, Blackstone EH, Kirklin JW: Complement activation during cardiopulmonary bypass: evidence for generation of C3a and C5a anaphylatoxines. *N Engl J Med* 1981; **304:** 497–503
9. Kirklin JK, Westaby S, Blackstone EH, Kirklin JW, Chenoweth DE, Pacifico AD: Complement and the damaging effects of cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1983; **86:** 845–857
10. Addonizio VP Jr, Smith JB, Strauss JF III, Colman RW, Edmunds LH Jr: Thromboxane synthesis and platelet secretion during cardiopulmonary bypass with bubble oxygenator. *J Thorac Cardiovasc Surg* 1980; **79:** 91–96
11. Hashimoto K, Miyamoto H, Suzuki K, Horikoshi S, Matsui M, Arai T, et al: Evidence of organ damage after cardiopulmonary bypass: The role of elastase and vasoactive mediators. *J Thorac Cardiovasc Surg* 1992; **104:** 666–673
12. Christakis GT, Fremes SE, Jean-Paul K, Harwood S, Juhasz S, Sharpe E, et al: Determinants of low systemic vascular resistance during cardiopulmonary bypass. *Ann Thorac Surg* 1994; **58:** 1040–1049
13. Downing SW, Edmunds H Jr: Release of vasoactive substances during cardiopulmonary bypass. *Ann Thorac Surg* 1992; **54:** 1236–1243
14. Lehot JJ, Villard J, Piriz H, Phibin DM, Carry PY, GauquelinG, et al: Hemodynamic and hormonal responses to hypothermic and normothermic cardiopulmonary bypass. *J Cardiothorac Anesth* 1992; **6:** 132–139
15. Frering B, Philip I, Dehoux M, Rolland C, Langlois JM, Desmonts JM: Circulating cytokines in patients undergoing normothermic cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1994; **108:** 636–641
16. Massimino RJ, Stearns GT, Gough JD, Martin J, Singh AK: Moderate hypothermic versus normothermic total cardiopulmonary bypass for coronary artery surgery: Retrospective study. *J Extra Corporeal Technol* 1991; **23:** 5–8
17. Birdi I, Regragui IA, Izzat MB, Alonso C, Black AMS, Bryan AJ, et al: Effects of cardiopulmonary bypass temperature on pulmonary gas exchange after coronary artery operations. *Ann Thorac Surg* 1996; **61:** 118–122
18. O'Dwyer C, Woodson LC, Conroy BP, Lin CY, Deyo DJ, Uchida T, et al: Regional perfusion abnormalities with phenylephrine during normothermic bypass. *Ann Thorac Surg* 1997; **63:** 728–735
19. Lyons C, Clark LC Jr, McDowell H, McArthur K: Cerebral venous oxygen content during carotid thrombectomy. *Ann Surg* 1964; **160:** 561–567
20. Clauss RH, Hass WK, Ransohoff J: Simplified method for monitoring adequacy of brain oxygenation during carotid artery surgery. *N Engl J Med* 1965; **273:** 1127–1131
21. Cook DJ, Oliver WC, Orszulak TA, Daly RC: A prospective, randomized comparison of cerebral venous oxygen saturation during normothermic and hypothermic cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1994; **107:** 1020–1029
22. Croughwell N, Smith LR, Quill T, Newman M, Greeley W, Kern F, et al: The effect of temperature on cerebral metabolism and blood flow in adults during cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1992; **103:** 549–554
23. Mora CT, Henson MB, Weintraub WS, Murkin JM, Martin TD, Craver JM, et al: The effect of temperature management during cardiopulmonary bypass on neurologic and neurophychologic outcomes in patients undergoing coronary revascularization. *J Thorac Cardiovasc Surg* 1996; **112:** 514–522
24. Regragui I, Birdi I, Izzat MB, Black AMS, Lopatatzidis A, Day CJE, et al: The effects of cardiopulmonary bypass temperature on neuropsychologic outcome after coronary artery operations: A prospective randomized trial. *J Thorac Cardiovasc Surg* 1996; **112:** 1036–1045
25. Plourde G, Leduc AS, Morin JE, DeVarennes B, Latter D, Symes J, et al: Temperature during cardiopulmonary bypass for coronary artery operations does not influence postoperative cognitive function: A prospective, randomized trial. *J Thorac Cardiovasc Surg* 1997; **114:** 123–128
26. Buschbeck D, Riess FC, Dobritzsch B, Dahme B, Bleese N: Short-term neuropsychologic differences after normothermic versus hypothermic cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1998; **116:** 350–353