Original Research

Relationship of Internal Jugular Venous Oxygen Saturation and Perfusion Flow Rate in Children and Adults During Normothermic and Hypothermic Cardiopulmonary Bypass

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Introduction: This study was designed to elucidate the trends in cerebral venous oxygen saturation in cyanotics and acyanotics undergoing normothermic and hypothermic cardiopulmonary bypass (CPB) and its relationship to perfusion flow rates.

Methods: Five hundred and forty-eight patients (253 cyanotics) undergoing first surgical correction using CPB were included in this prospective study. One hundred and seventy-two patients underwent surgical correction under normothermic CPB (34-36˚C) - group I; 142 patients were operated under moderately hypothermic CPB - group II; and 234 patients were operated under deep hypothermic CPB - group III. The perfusion flow rates were adjusted to maintain the internal jugular venous oxygen saturation ($IJVO_2$) between 70-80% in both cyanotics and non-cyanotics.

Results: The prevalence of preoperative cerebral venous desaturation was 17.4% and 5.1% in cyanotic and acyanotic groups, respectively. All patients undergoing hypothermic CPB had $IJVO_2$ >75% at the recommended perfusion flow rate. During surgery, 87.2% of group I patients undergoing normothermic CPB and 88.5% of group II and III patients undergoing hypothermic CPB had $IJVO_2$ <75% during re-warming and required an increased perfusion flow rate to maintain $IJVO_2$ >75%. The cyanotics demonstrated a higher incidence of cerebral desaturation in all three groups. Patients aged <4 years had almost the same prevalence of cerebral desaturation compared to the older patients.

Conclusions: We conclude that patients undergoing normothermic CPB are at greater risk of cerebral desaturation. The cyanotics are at greater risk compared to acyanotics during normothermic CPB and during the re-warming phase of hypothermic CPB and require an individualised increased perfusion flow rate.

Despite technical advances in cardiovascular surgery and a dramatic reduction in mortality over the past decade, neurological abnormalities suggestive of hypoxia-ischaemia continue to be the major cause of morbidity in 5% to 25% of patients undergoing open heart surgery.[1-3] Currently, the most effective means of cerebral protection from cardiopulmonary bypass (CPB) or deep hypothermic circulatory arrest-induced injury is hypothermia.[4,5] Previous investigators have demonstrated different calculated flow requirements based on bodyweight, body surface area, and core temperature.[3-6]

A wealth of previous investigations support the possibility that factors critical to cerebral protection during bypass support are distinctly different for patients at the extremes of the age range.[1-6] Jugular blood desaturation represents an imbal-

ance in cerebral oxygen supply and demand that occurs during normothermic CPB and the re-warming phase of hypothermic CPB and may represent transient cerebral ischaemia.[7-10]

The aetiology of neurological injury during CPB is multi-factorial and, as yet, there is no foolproof formula for determining the degree of cerebral venous desaturation responsible for a reversible or irreversible cerebral ischaemic insult. Lyons and Clauss demonstrated a statistically significant increase in neurodeficit in patients undergoing carotid artery surgery with a jugular venous oxygen ($IJVO_2$) pressure <25 mmHg and $IJVO_2$ saturation <60%.[11,12] There have been reports suggesting that normothermic CPB may be associated with a higher prevalence of neurological injury.[5,6]

With this background, we hypothesised that a cerebral blood flow-metabolism imbalance occurring during bypass support might be mitigated by increased perfusion flow, and that there could be a minimum safe pump flow necessary at a particular temperature in order to maintain cerebral oxygenation during CPB, thus preventing hypoxic cerebral injury. The available literature does not address the normal $IJVO_2$ saturation, the amount of additional flow required in an individual patient to maintain optimal cerebral oxygenation, and the difference in basal cerebral oxygenation and cerebral oxygen extraction, if any, between cyanotics and acyanotics.

This prospective study aimed to: i) elucidate the basal cerebral venous oxygen saturation trends in cyanotics and acyanotics undergoing corrective cardiac surgical procedures under CPB; ii) assess and compare the $IJVO_2$ saturation and cerebral arteriovenous oxygen saturation difference in patients undergoing normothermic and hypothermic CPB; iii) identify the subset of patients undergoing corrective cardiac surgery under normothermic or hypothermic CPB who are at an increased risk for sustained intraoperative cerebral desaturation; and iv) finally, investigate the relationship, if any, between oxygen saturation of the internal jugular venous blood, cerebral arteriovenous oxygen saturation difference, and perfusion flow rates during CPB during normothermia and hypothermia in both cyanotics and acyanotics.

Methods

This study conforms to the principles outlined in the declaration of Helsinki. Five hundred and forty-eight patients (74.6% males) scheduled to undergo first surgical correction under CPB between January 2006 and June 2008 were enrolled in this prospective, non-randomised trial after Institutional Ethics Committee approval and written informed consent from each patient had been obtained. The patients' demographic and clinical profiles are given in Tables 1 and 2.

Based on the severity of cardiac disease and the requirement to surgically correct the same at a particular desired core temperature, the patients were each allocated to one of three groups:

- Group I (normothermic bypass group; nasopharyngeal temperature maintained between 34-36°C) (n=172) included patients undergoing atrial septal defect closure (n=33), pulmonary valvotomy (n=5), mitral valve reconstruction (n=24), mitral valve replacement (MVR) (n=72), bi-directional superior cavopulmonary connection (SCPC) (n=38).
- Group II (moderately hypothermic bypass group; lowest nasopharyngeal temperature 30°C) (n=142) included patients undergoing isolated aortic valve replacement (AVR) (n=18), AVR with concomitant coronary artery bypass grafting (CABG) (n=4), CABG (n=38), total cavopulmonary connection (TCPC) (n=40), ventricular septal defect closure (n=31), right ventricular outflow tract resection (n=11), cardiac tumour resection (n=1).
- Group III (deep hypothermic bypass group; lowest nasopharyngeal temperature 28°C) (n=234) included patients undergoing intracardiac repair of tetralogy of Fallot (TOF) (n=150), rechannelling of totally anomalous pulmonary venous connection (TAPVC) (n=11), arterial switch operation/ Senning's procedure (n=9), combined aortic and mitral valve replacement (n=56), and Bentall's procedure for annuloaortic ectasia, acute and chronic ascending aortic dissection (n=8).

Of the 548 patients, 253 (46.2%) had different types of cyanotic congenital heart diseases. Patients with pulmonary, neurological, or craniofacial disease, genetic abnormality associated with a brain malformation and history of birth asphyxia were excluded from this study.

Internal jugular vein sampling

The anaesthetic technique was standardised for all patients. The depth of anaesthesia was monitored in all patients with the help of Bispectral index (BIS) monitoring (BIS™ Monitor Model A-2000, Aspect

Table 1. Demographic, haemodynamic and cardiopulmonary bypass-related data of the normothermic and hypothermic study groups

Variables	Group I	Group II	Group III	p
Number of patients	172	142	234	
Age in months				
mean ± SD	67.81 ± 87.11	60.97 ± 77.55	59.11 ± 70.77	
(95% CI)	(54.70-80.92)	(48.10-73.83)	(53.17-65.04)	0.07
Range	2-480	3-648	2-648	
Weight in kg				
mean ± SD	37.53 ± 19.80	36.83-24.54	30.24 ± 18.71	
(95% CI)	(34.54-40.51)	(32-76-40.90)	(27.83-32.65)	0.001
Range	7-110	4-98	6-89	
Body surface area (m^2)				
mean ± SD	1.19 ± 0.45	1.21 ± 1.06	1.03 ± 0.45	
(95% CI)	(1.13-1.27)	(1.04-1.39)	(0.97-1.09)	**0.01**
Range	0.24-2.18	0.19-12.02	0.30-2.10	
NYHA functional class III/IV	125 (57.6%)	105 (73.9%)	180 (76.9%)	0.001
Preoperative haemoglobin, g (%)				
mean ± SD	13.77 ± 3.49	13.35 ± 2.80	16.74 ± 3.63	
(95% CI)	(13.25-14.30)	(12.89-13.82)	(16.27-17.21)	**<0.001**
Range	10-28.9	10-22	11-24	
Preoperative internal jugular venous oxygen saturation (%)				
mean ± SD	71.85 ± 7.49	70.84 ± 9.59	72.52 ± 9.86	
(95% CI)	(70.73-72.98)	(69.25-72.43)	(68.29-76.75)	0.78
Range	55-90	53-92	40-90	
Perfusion flow rate during cooling(I), ($L.min^{-1}.m^{-2}$)				
mean ± SD		2.88 ± 1.16	2.79 ± 0.88	
(95% CI)	–	(2.69-3.07)	(2.68-2.91)	0.38
Range		0.6-4.9	0.9-5.0	
Intraoperative internal jugular venous oxygen saturation(%) cooling I				
mean ± SD		73.65 ± 7.78	74.17 ± 7.05	
(95% CI)	–	(72.36-74.94)	(73.26-75.08)	0.50
Range		53-94	45-94	
Perfusion flow rate during cooling(II), ($L.min^{-1}.m^{-2}$)				
mean ± SD		2.92 ± 1.17	2.80 ± 0.87	
(95% CI)	–	(2.73-3.12)	(2.68-2.91)	0.24
Range		0.6-4.9	0.9-5.0	
Intraoperative internal jugular venous oxygen saturation(%) cooling II				
mean ± SD		74.83 ± 9.51	80.15 ± 6.29	
(95% CI)	–	(73.26-76.41)	(74.18-86.11)	0.17
Range		6-91	56-778	
Perfusion flow rate during warming(I), ($L.min-1.m^2$)				
mean ± SD	3.13 ± 0.99	2.95 ± 1.17	2.81 ± 0.88	
(95% CI)	(2.98-3.28)	(2.76-3.15)	(2.70-2.92)	**0.006**
Range	1-10	1-5	1-5	
Intraoperative internal jugular venous oxygen saturation(%) warming I				
mean ± SD	63.62 ± 8.23	60.94 ± 9.02	63.10 ± 9.02	
(95% CI)	(62.38-64.86)	(59.44-62.43)	(61.94-64.27)	**0.018**
Range	50-85	11-84	48-88	

Variables	Group I	Group II	Group III	p
Perfusion flow rate during warming(II) (min^{-1}, m^{-2})				
mean ± SD	3.42 ± 0.88	3.27 ± 1.25	3.14 ± 0.91	
(95% CI)	(3.29-3.55)	(3.06-3.48)	(3.03-3.26)	**0.024**
Range	1.2-5.6	0.6-5.6	1.2-5.6	
Intraoperative internal jugular venous oxygen saturation(%) warming II				
mean ± SD	78.11 ± 5.92	76.50 ± 8.81	78.25 ± 7.61	
(95% CI)	(77.22-79.01)	(75.04-75.96)	(77.27-79.23)	0.066
Range	60-88	44-89	51-90	
Post bypass internal jugular venous oxygen saturation (%)				
mean ± SD	75.93 ± 5.00	74.92 ± 5.61	76.06 ± 5.47	
(95% CI)	(75.18-76.69)	(73.99-75.85)	(75.35-76.76)	0.113
Range	58-89	58-90	58-91	
Preoperative systemic arterial oxygen saturation (%),				
mean ± SD	91.50 ± 7.07	93.76 ± 5.13	90.51 ± 6.41	
(95% CI)	(90.43-92.56)	(92.91-94.61)	(89.68-91.34)	**<0.001**
Range	50-100	79-100	73-100	
Preoperative cerebral (a-v)O_2 saturation				
mean ± SD	19.85 ± 7.43	22.92 ± 9.69	17.99 ± 34.49	
(95% CI)	(18.73-20.97)	(21.31-24.53)	(13.68-23.30)	0.13
Range	4-43	11-55	13-60	
Cerebral (a-v)O_2 saturation during cooling				
mean ± SD		20.10 ± 8.84	16.34 ± 9.7	
(95% CI)	–	(18.64-21.57)	(15.09-17.58)	**<0.001**
Range		2-47	5-55	
Cerebral (a-v)O_2 saturation during warming (I)				
mean ± SD	27.92 ± 8.7	32.82 ± 10.36	27.41 ± 12.39	
(95% CI)	(26.60-29.24)	(31.10-34.54)	(25.81-29.00)	**<0.001**
Range	4-46	8-98	13-52	
Cerebral (a-v)O_2 saturation during warming (II)				
mean ± SD	14.50 ± 8.17	17.26 ± 10.67	12.26 ± 11.12	
(95% CI)	(13.27-15.73)	(15.49-19.03)	(10.83-13.69)	**<0.001**
Range	10-40	11-55	13-52	
Post bypass cerebral (a-v)O_2 saturation				
mean ± SD	15.96 ± 7.32	18.84 ± 7.30	14.45 ± 9.15	
(95% CI)	(14.86-17.06)	(17.63-20.05)	(13.27-15.63)	**<0.001**
Range	13-33	11-42	6-40	
Intraoperative internal jugular venous oxygen saturation <75% during normothermic CPB and during initial re-warming (phase I) of hypothermic CPB requiring increased perfusion flow rate				
Age <48 months	87 (77.7%)	60 (88.2%)	130 (85.5%)	
Age >48 months	51 (85%)	68 (91.9%)	66 (80.5%)	–
p-value	0.25	0.46	0.32	

(a-v)O_2 saturation – arteriovenous oxygen saturation difference.

Medical Systems, Inc., Newton MA, USA). For adequate depth of anaesthesia a BIS value of 30-50 was maintained in all patients. After induction of anaesthesia, a 20-22 Fr long indwelling cannula (Arrow International, Bernville Road Reading PA, USA) was passed into the jugular bulb retrogradely from the high internal jugular vein puncture for sampling and monitoring of internal jugular venous oxygen ($IJVO_2$). Proper catheter placement "in the jugular bulb" was confirmed by fluoroscopy and contrast injection. Heart rate, arterial, pulmonary artery and right atrial pressures, end-tidal CO_2 and nasopharyngeal temperature were monitored along with $IJVO_2$.

Heparin and protamine management

Heparin was given at a dose of 3 mg/kg to achieve a target activated clotting time (ACT) between 480-600 seconds before commencement of CPB. The ACT was monitored every thirty minutes during CPB and an additional 0.5 mg/kg heparin was administered if required. Protamine was used to reverse the effect of heparin at a dose ratio of 1.5:1.

Cardiopulmonary bypass management

The cardiopulmonary bypass technique was standardised as much as possible between the study groups, except for pump flow and core temperature. The duration of CPB varied depending on the surgical repair.

All patients were operated under CPB using aortobicaval cannulation. The extracorporeal device consisted of a roller pump (Sarns 9000; Sarns 3M Health Care Cardiovascular Systems, Ann Arbor MI, USA), heat exchanger (Terumo Sarns TCM II, Ann Arbor MI, USA), membrane oxygenator (Medtronic Minimax Plus, Medtronic Inc., Minneapolis MN, USA) and online arterial filters (Affinity, Medtronic Inc, Minneapolis MN, USA). The primer of the circuit consisted of 1800 ml of Ringer's lactate in the adult population and 1000 ml in the paediatric population, containing 0.5 g/kg of mannitol and 5000 units of heparin. The haematocrit was maintained between 0.25-0.30 in all patients during CPB. The pump flows were adjusted to maintain a cardiac index greater than 2.4 l/min/m^2 in adult patients. In paediatric patients, flows were given at 150-200 ml/kg. Additional flows were given to maintain $IJVO_2$ saturation above 75% whenever required. Myocardial protection was achieved by intermittent antegrade administration of a cold St. Thomas-based cardioplegic solution along with local cooling and repeated every 20 minutes.

Management of CPB, pump flow and perfusate temperature were as follows: in the normothermic CPB group, arterial perfusate temperature was maintained between 34°C and 36°C and the pump flows were initially maintained at the recommended flow rate. In the hypothermic CPB group, the initial arterial perfusate temperature was 25°C until the nasopharyngeal temperature reached either 28°C or 30°C, as desired in an individual patient. When nasopharyngeal temperature reached 28-30°C as desired, the pump flow was decreased to 150 ml/min/m^2 in children and 2.0 L/min/m^2 in adults. During re-warming, pump flow was increased to 150-200 ml/min/m^2 in children and 2.4 L/min/m^2 in adults. Our aim was to maintain $IJVO_2$ saturation between 70-80% at all phases of CPB. Pump flows were increased by 10-40%, if needed, to maintain $IJVO_2$ saturation between 70-80% in all cases. FIO_2/Sweep gas was kept constant to maintain the desired $IJVO_2$ concentration. Blood gas management was done by alpha stat in patients cooled up to 30°C and by pH stat in cyanotic patients cooled up to 28°C.

Nitroglycerine infusion was used during CPB to maintain mean arterial pressures of 45-70 mmHg. CPB was discontinued after the cardiovascular lesion was repaired, haemodynamics and pulmonary function were acceptable, and nasopharyngeal temperature reached 34°C.

Study protocol

Arterial O_2 saturation (SaO_2) and $IJVO_2$ were measured by blood gas analyser (Model-Stat Profile® M Blood Gas and Electrolyte Analyser, Nova Biomedical Corporation, Waltham MA, USA). Cerebral arteriovenous oxygen saturation difference [$S(a\text{-}v)O_2$] was calculated as the difference of SaO_2 and $IJVO_2$ [$S(a\text{-}v)O_2 = SaO_2 - IJVO_2$].

Baseline SaO_2 and $IJVO_2$ were obtained after induction of anaesthesia and before the onset of CPB, when all patients were in a haemodynamically stable condition (period I). Changes in $IJVO_2$ were recorded at least twice during the initial cooling period (period II) and during hypothermia at 28°C or 30°C (period III), twice during re-warming (period IV and V), and at 45 minutes after weaning from CPB, when haemodynamics, ventilation and haematocrit values were again in a steady state (period VI).

In the normothermic bypass group, samples for periods I, III, IV, V and VI were taken at 15, 30 and 45 minutes of CPB. If the estimated $IJVO_2$ saturation

was below 70-80%, the flow was increased proportionately to achieve the desired effect.

Other CPB factors controlling cerebral O_2 extraction – haemoglobin, perfusion flow, perfusate temperature, haematocrit, partial pressure of oxygen and carbon dioxide – were also recorded at baseline, during cooling, re-warming and after CPB had been discontinued.

Outcome variables

In the 548 patients, there were 20 (3.6%) perioperative and 3 (0.5%) late deaths. Risk factors for in-hospital deaths were analysed. The possible side effects of the flow-adapted regime, e.g. haemolysis, transfusion requirements, more inflammatory reaction and capillary leakage, were noted.

Demographic data were also noted, including duration of CPB, cardiovascular lesion and neurological status for 2 days after the operation. Neurological status was judged as normal or abnormal on the basis of physical examination by the ICU physician. Abnormal was defined as the presence of seizures, stroke or coma (prolonged loss of consciousness, lasting >24 hours after the operation). No formal neuropsychological testing was done to compare the clinical outcome in the three groups.

Collection of the data as outlined above allowed the following comparisons to be made: (i) basal cerebral venous oxygen saturation trends in cyanotics and acyanotics undergoing corrective cardiac surgery; (ii) $IJVO_2$, cerebral arteriovenous oxygen saturation difference in normothermic and both hypothermic groups in each of the six study periods; (iii) the percentage of patients in each group of both cyanotics and acyanotics demonstrating cerebral venous desaturation ($IJVO_2$ <60%) during each of the three CPB periods; (iv) examination of $IJVO_2$ trends in each group during CPB; (v) correction of perfusion flow rate and $IJVO_2$ saturation at different stages of CPB among three groups of patients and between cyanotics and acyanotics; and (vi) the requirement to increase perfusion flow to maintain optimal cerebral oxygenation during periods of jugular venous desaturation in cyanotics versus acyanotics and in patients undergoing normothermic versus hypothermic CPB.

Statistical analysis

The statistical analysis was performed using inter-cooled STATA 9.0 software (STATA Corp., College station, TX 77845, USA). Descriptive statistics were calculated for continuous and categorical variables. The Student t-test was used to identify significant differences between 2 groups for continuous variables. Repeated measures 2-way analysis of variance (ANOVA) with the Bonferroni *post hoc* test was used to assess the influence of perfusion flow rate and other variables on $IJVO_2$ at different stages of CPB among different group of patients and between the cyanotics and non-cyanotics. Percentage changes between the preoperative, intraoperative and postoperative values for $IJVO_2$ and cerebral arteriovenous oxygen saturation difference were calculated and compared by one-way ANOVA with *post hoc* (least significant difference) analysis for the 3 groups. The χ^2 test was used to identify associations among the groups for categorical variables.

The correlation between $IJVO_2$, cerebral arteriovenous oxygen saturation difference and perfusion flow rates at different stages of CPB among different groups of patients and between cyanotics and acyanotics was assessed using Pearson's correlation coefficient (r). A p-value <0.05 was considered significant.

Results

There were 20 early deaths (3.6%) and 3 (0.5%) late deaths. Three patients were lost to follow up. The perioperative deaths were due to low output syndrome (group I, n=2; group II, n=2), malignant ventricular arrhythmias (group II, n=2; group III, n=1), massive pulmonary bleeding (group III, n=2), renal failure (group II, n=2), respiratory insufficiency (group III, n=1), global hypoxic-ischaemic cerebral injury (group II, n=1; group III, n=5) and multi-organ failure (group III, n=2). The distribution of the deaths with respect to disease was as follows: MVR, n=2; SCPC, n=1; CABG, n=3; TCPC, n=2; TOF, n=5; combined AVR & MVR, n=3; Bentall's procedure, n=1; rechannelling of TAPVC, n=2; resection of cardiac tumour, n=1. Of the 6 patients who died from global hypoxic-ischaemic cerebral injury, 1 patient had undergone CABG, 1 patient had rechannelling of TAPVC, and 4 patients had intracardiac repair of TOF. Incidentally, despite the increased perfusion flow rate, all patients dying primarily of neurological causes had $IJVO_2$ between 60-75%.

Two patients (combined AVR & MVR, n=1; AVR & CABG, n=1) with embolic stroke and one patient (isolated AVR, n=1) with refractory ventricular ar-

rhythmias died late postoperatively. Four patients with mechanical prosthetic valve replacements (DVR, n=2; MVR, n=2) had thromboembolic complications. Three recovered with residual weakness and one recovered completely.

Follow up was 99.4% complete (522 of 525; range 1-30 months) and yielded 836.50 patient-years of data with a mean follow-up time of 19.23 months (± SD 7.46; median 21 months). The actuarial survival at 30 months was 95.6 ± 0.009%.

Preoperatively, 17.4% of the cyanotic group and 5.1% of the acyanotic group exhibited $IJVO_2$ ≤60% ($p<0.001$). Mean basal $IJVO_2$ in cyanotic and acyanotic patients was 70.62 ± 31.64 and 72.95 ± 8.52, respectively; the difference was not statistically significant. The requirement to increase perfusion flow rate to maintain $IJVO_2$ >75% was maximal during the initial part of the re-warming phase of patients undergoing hypothermic CPB ($p=0.006$). Like cyanotics, the acyanotic group of patients also required an increased perfusion flow rate to maintain $IJVO_2$ >75%. However, the cyanotic group of patients required a greater increase in perfusion flow compared to the acyanotics (Tables 1, 2; Figures 1-3).

During the cooling phase, there was no significant difference in perfusion flow rate requirement to maintain $IJVO_2$ >75% in patients undergoing surgery under mild or moderate hypothermia. During the re-warming phase, 93% (n=132) of group II and 85.9% (n=201) of group III patients required an increased perfusion flow to maintain $IJVO_2$ >75%. It is noteworthy that 87.2% (n=150) patients of group I, undergoing normothermic CPB, also required an increased perfusion flow to maintain $IJVO_2$ >75%. The increase in perfusion flow requirement was statistically significant in group I patients as compared to patients in groups II and III (Tables 1-5).

Preoperatively, 13.2% (n=31), 11.3% (n=16) and 7% (n=12) patients of groups III, II and I, respectively, exhibited an $IJVO_2$ below 60% and there was no statistically significant difference between the groups. During surgery, 47.1% (n=81) of patients undergoing normothermic CPB, 65.5% (n=93) and 56% (n=131) of patients undergoing hypothermic CPB exhibited $IJVO_2$ below 60% ($p=0.005$) (Table 3). The cyanotics demonstrated a higher incidence of cerebral venous desaturation as compared to acyanotics in all three groups, irrespectively of core temperature. It is noteworthy that the normothermic bypass group (group I) demonstrated a higher incidence of cerebral venous desaturation as compared to the deep hypothermic bypass group (group III) (Table 6).

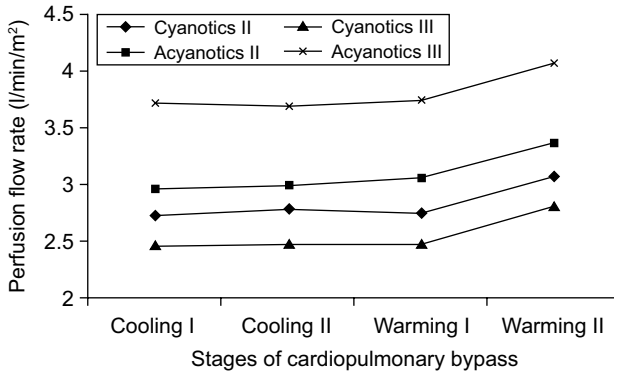

Figure 1. Mean perfusion flow rate in cyanotics and acyanotics at different stages of cardiopulmonary bypass for groups II and III. $p<0.001$ by Student's t-test.

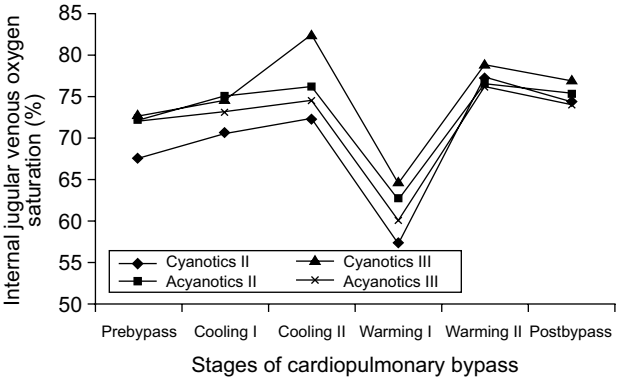

Figure 2. Mean internal jugular venous oxygen saturation ($IJVO_2$) in cyanotics and acyanotics at different stages of cardiopulmonary bypass for groups II and III. $p=0.02$ during re-warming.

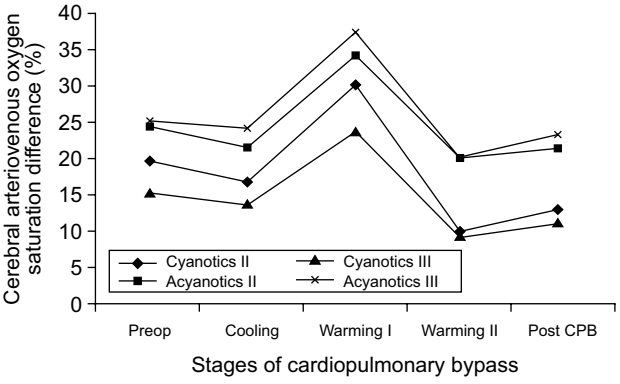

Figure 3. Mean cerebral arteriovenous oxygen saturation difference, $(a\text{-}v)O_2$, in cyanotics and acyanotics at different stages of cardiopulmonary bypass for groups II and III. $p<0.001$ for group III during re-warming.

Table 2. Demographics, preoperative and intraoperative characteristics of the study group.

	Cyanotics	Acyanotics	p
Number of patients, n (%)	253 (46.2%)	295 (53.8%)	
Age (months)	70.47 ± 4.43	56.69 ± 71.07	0.38
Weight (kg)	20.80 ± 45.76	12.53 ± 19.83	**<0.001**
Body surface area (m^2)	0.86 ± 1.36	0.79 ± 0.43	**<0.001**
Preoperative haemoglobin (g%)	18.27 ± 2.91	12.07 ± 0.87	**<0.001**
Systemic arterial oxygen saturation (%)	86.91 ± 6.11	95.73 ± 3.06	**<0.001**
Perfusion flow rate during cooling ($L.min^{-1}.m^{-2}$)			
I	2.50 ± 0.75	3.24 ± 1.11	**<0.001**
II	2.52 ± 0.75	3.25 ± 1.12	**<0.001**
Perfusion flow rate during warming ($L.min^{-1}.m^{-2}$)			
I	2.46 ± 0.88	3.36 ± 0.91	0.80
II	2.75 ± 0.80	3.71 ± 0.96	0.69
Internal jugular venous oxygen saturation ($IJVO_2$) (%)			
Pre-bypass (Baseline)	70.62 ± 31.64	72.95 ± 8.52	0.19
Cooling (I)	73.79 ± 6.63	74.22 ± 8.14	**0.04**
Cooling (II)	80.33 ± 48.77	75.36 ± 9.59	0.69
Warming I	62.13 ± 9.28	63.20 ± 8.41	0.53
Warming II	78.46 ± 6.76	77.15 ± 8.02	0.61
Post-bypass	75.96 ± 5.15	75.52 ± 5.57	0.31
Cerebral (a-v)O_2 saturation difference (%)			
Pre-bypass (Baseline)	16.44 ± 31.38	22.78 ± 9.28	0.21
Cooling	14.07 ± 8.35	22.43 ± 8.87	0.47
Warming I	24.81 ± 11.24	32.54 ± 9.59	0.63
Warming II	9.21 ± 9.28	18.58 ± 9.19	0.29
Post-bypass	11.22 ± 7.35	20.21 ± 6.17	**0.003**
Internal jugular venous oxygen saturation (<60%), No. (%)			
Pre-bypass (Baseline)	44 (17.4%)	15 (5.1%)	**<0.001**
Cooling I	5 (2.4%)	10 (6%)	0.07
Cooling II	3 (1.4)	9 (5.4%)	**0.03**
Warming I	144 (56.9%)	161 (54.6%)	0.58
Warming II	1 (0.4%)	6 (2%)	0.08
Post-bypass	4 (1.6%)	7 (2.4%)	0.51
Internal jugular venous oxygen saturation (<75%), No. (%)			
Pre-bypass (Baseline)	202 (79.8%)	177 (60 %)	**0.001**
Cooling I	114 (54.3%)	80 (48.21%)	0.24
Cooling II	72 (34.3%)	66 (39.81%)	0.27
Warming I	225 (88.9%)	258 (87.5%)	0.59
Warming II	67 (26.5%)	80 (27.1%)	0.86
Post-bypass	99 (39.1%)	112 (38%)	0.78

(a-v)O_2 saturation – arteriovenous oxygen saturation difference.

Cerebral arteriovenous oxygen saturation difference was maximal during normothermic CPB and during the initial re-warming phase of hypothermic CPB. Group I and II patients had a higher oxygen saturation difference as compared to group III patients. Like cyanotics, the acyanotics had an almost equal tendency for increased cerebral oxygen extraction and there was no statistically significant difference between the groups. After weaning from CPB, both cyanotics and acyanotics exhibited greater $IJVO_2$ saturation and cerebral arteriovenous oxygen saturation difference as compared to the preoperative values (Table 1).

In this study, 60.6% (332 of 548) patients (group I, n=112; group II, n=68; and group III, n=152) were <48 months of age. During the re-warming phase of hypothermic CPB and during normothermia, 277

(83.4%: group I, n=87; group II, n=60; group III, n=130) patients aged <48 months and 185 (85.6%: group I, n=51; group II, n=68; group III, n=66) patients aged >48 months required an increased perfusion flow rate to maintain $IJVO_2$ >75%. The difference in the requirement for an increase in perfusion flow between the two age groups was statistically non-significant in all three groups.

Discussion

The major finding of this investigation was a consistent increase in internal jugular venous oxygen saturation during bypass cooling of both cyanotics and acyanotics undergoing hypothermic CPB. The second important finding was a consistent decrease in $IJVO_2$ saturation during bypass re-warming in both cyanotics and acyanotics. Like cyanotics, the acyanotics had an almost equal tendency for cerebral oxygen extraction and there was no statistically significant difference between the groups. The third important finding was the requirement to increase perfusion flow rate in 87.2% of patients undergoing surgery under normothermia in order to maintain the desired $IJVO_2$ oxygenation (75-80%). The fourth important finding was the requirement to increase pump flow during bypass re-warming in 88.9% of cyanotics and 87.5% of acyanotics in order to achieve the desired $IJVO_2$ concentration (75-80%).

Perfusion flow rate and jugular venous oxygenation in patients aged less than versus more than 4 years, cyanotics versus acyanotics, under normothermic versus hypothermic CPB

The available literature does not address the interrelationship between the degree of jugular venous desaturation and episodes of cerebral ischaemia. Based on the observations of Lyons and Clauss, jugular bulb venous oxygen desaturation was defined as $PIJVO_2$ of <25 mmHg or $SIJVO_2$ <60% in the present study.[11,12]

In this study, 277 (83.4%) patients aged <48 months and 185 (85.6%) patients aged >48 months had $IJVO_2$ <75% during normothermic CPB and the re-warming phase of hypothermic CPB and required an increased perfusion flow rate. Pairwise comparisons of the increased perfusion flow requirements between the two age groups showed marginal differences in all 3 groups of patients that were not statistically significant (Table 1).

Overall, 17.4% of the cyanotic group, 5.1% of the acyanotic group, 7% of the normothermic group and 12.5% of the hypothermic group had cerebral venous desaturation ($IJVO_2$ <60%) in the preoperative period. The mean basal $IJVO_2$ in cyanotic and acyanotic patients was 70.62 ± 31.64 and 72.95 ± 8.52, respectively, and the difference was not statistically significant (Tables 1-6). The question is whether this subset of patients with pre-existing cerebral desaturation are at greater risk of perioperative hypoxic-ischaemic damage. Published results, including the data in this manuscript, do not provide any conclusive answer to this question.

It is noteworthy that the three groups of patients in this study had varying combinations of cyanotic and acyanotic heart diseases. During surgery, 87.2% of patients undergoing normothermic CPB and 88.5% of patients undergoing hypothermic CPB had $IJVO_2$ below 75% during re-warming and required an increased perfusion flow rate to maintain the desired $IJVO_2$ between 75-80% (Table 3). Despite the increased perfusion flow rate, 22.7% of patients undergoing normothermic CPB and 28.7% of patients undergoing hypothermic CPB continued to exhibit low cerebral venous saturation (<75%) (Table 3).

Like cyanotics, the acyanotic group of patients also required an increased perfusion flow rate to maintain cerebral oxygenation ($IJVO_2$ >75%). However, the cyanotic patients required a greater increase in perfusion flow rate as compared to acyanotics. Pairwise comparisons between cyanotic and acyanotic patients of three different groups during different stages of CPB demonstrated an increased requirement in terms of perfusion flow rate to maintain $IJVO_2$ >75% in 88.9% and 87.5% of cyanotic and acyanotic group of patients, respectively. After the reparative surgical procedure, 4 (1.6%) patients of the cyanotic group and 7 (2.4%) patients of the acyanotic group continued to have persistent cerebral desaturation ($IJVO_2$ <60%). Among the multi-factorial causes of cerebral injury, biological variability of cerebral metabolic rates between individuals may be the possible causative factor for persistent desaturation (Table 1).

Perfusion flow rate and cerebral arteriovenous oxygen saturation in cyanotics and acyanotics during normothermic and hypothermic CPB

In this study, the mean preoperative basal cerebral arteriovenous oxygen saturation difference among cyanotics and acyanotics was 16.44 ± 31.38 and 22.78 ± 9.28, respectively (p=0.21) (Table 1). There was maximal cerebral oxygen extraction during normothermic CPB and during bypass re-warming in all patients of the study group. By pairwise compari-

Table 3. Distribution of patients with internal jugular venous oxygen saturation ≤60% (A) and ≤75% (B) during different phases of cardiopulmonary bypass in the three groups of patients

A. Internal jugular venous oxygen saturation ≤60%				
Parameters	Group I (n=172)	Group II (n=142)	Group III (n=234)	p
Pre-bypass	12 (7.0%)	16 (11.3%)	31 (13.2%)	0.12
Cooling I	–	6 (4.2%)	9 (3.8%)	0.85
Cooling II	–	7 (4.9%)	5 (2.1%)	0.13
Warming I	81 (47.1%)	93 (65.5%)	131 (56.0%)	**0.005**
Warming II	0	3 (2.1%)	4 (1.7%)	0.18
Post-bypass	3 (1.7%)	4 (2.8%)	4 (1.7%)	0.72
B. Internal jugular venous oxygen saturation ≤75%				
Parameters	Group I (n=172)	Group II (n=142)	Group III (n=234)	p
Pre-bypass	116 (67.4%)	99 (69.7%)	164 (70.1%)	0.84
Cooling I	–	75 (52.8%)	119 (50.9%)	0.71
Cooling II	–	65 (45.8%)	73 (31.2%)	**0.004**
Warming I	150 (87.2%)	132 (93.0%)	201 (85.9%)	0.11
Warming II	39 (22.7%)	42 (29.6%)	66 (28.2%)	0.32
Post-bypass	62 (36.0%)	64 (45.1%)	85 (36.3%)	0.17

Table 4. Distribution of patients with and without cyanosis with internal jugular venous oxygen saturation ≤60% (A) and ≤75% (B) during different phases of cardiopulmonary bypass in the three groups of patients.

A. Internal jugular venous oxygen saturation <60%									
Parameters	Group I			Group II			Group III		
	Cyanotics (n=43)	Acyanotics (n=129)	p	Cyanotics (n=40)	Acyanotics (n=102)	p	Cyanotics (n=170)	Acyanotics (n=64)	p
Pre-bypass (baseline)	10 (23.3%)	2 (1.6%)	**0.001**	9 (22.5%)	7 (6.9%)	**0.008**	25 (14.7%)	6 (9.4%)	0.28
Cooling I	–	–	–	0	6 (5.9%)	0.11	5 (2.9%)	4 (6.3%)	0.24
Cooling II	–	– –		0	7 (6.9%)	0.08	3 (1.8%)	2 (3.1%)	0.52
Warming I	29 (67.4%)	52 (40.3%)	**0.002**	31 (77.5%)	62 (60.8%)	**0.05**	84 (49.4%)	47 (73.4%)	**0.001**
Warming II	NIL	NIL	NIL	0	3 (2.9%)	0.27	1 (0.6%)	3 (4.7%)	**0.03**
Post-bypass	3 (7.0%)	–	**0.002**	0	4 (3.9%)	0.20	1 (0.6%)	3 (4.7%)	**0.03**
B. Internal jugular venous oxygen saturation <75%									
Parameters	Group I			Group II			Group III		
	Cyanotics (n=43)	Acyanotics (n=129)	p	Cyanotics (n=40)	Acyanotics (n=102)	p	Cyanotics (n=170)	Acyanotics (n=64)	p
Pre bypass (baseline)	41 (95.3%)	75 (58.1%)	**<0.001**	33 (82.5%)	66 (64.7%)	**0.03**	128 (75.3%)	36 (56.3%)	**0.005**
Cooling I	–	–	–	33 (82.5%)	42 (41.2%)	**<0.001**	81 (47.6%)	38 (59.4%)	0.11
Cooling II	–	–	–	30 (75.0%)	35 (34.3%)	**<0.001**	42 (24.7%)	31 (48.4%)	**<0.001**
Warming I	43 (100.0%)	107 (82.9%)	**0.004**	40 (100.0%)	92 (90.2%)	**0.04**	142 (83.5%)	59 (92.2%)	0.09
Warming II	10 (23.3%)	29 (22.5%)	0.9	10 (25%)	32 (31.4%)	0.45	47 (27.6%)	19 (29.7%)	0.75
Post bypass	23 (53.5%)	39 (30.2%)	**0.006**	21 (52.5%)	43 (42.2%)	0.26	55 (32.4%)	30 (46.9%)	**0.04**

Table 5. Pairwise comparisons of perfusion flow rate, SaO_2 saturation, internal jugular venous oxygen saturation, oxygen extraction and Hb (preoperative, intraoperative) in cyanotic and non-cyanotic patients of three different groups (n=548) during different phases of cardiopulmonary bypass

Variables	Group I			Group II			Group III		
	Cyanotics (n=43)	Acyanotics (n=129)	p	Cyanotics (n=40)	Acyanotics (n=102)	p	Cyanotics (n=170)	Acyanotics (n=64)	p
Perfusion flow rate									
– Cooling I	–	–	–	2.72 ± 0.69	2.95 ± 1.29	**<0.001**	2.45 ± 0.75	3.70 ± 0.44	**<0.001**
– Cooling II	–	–	–	2.76 ± 0.67	2.98 ± 1.31	**<0.001**	2.46 ± 0.75	3.68 ± 0.46	**<0.001**
– Warming I	2.19 ± 1.34	3.45 ± 0.58	**0.013**	2.74 ± 0.69	3.04 ± 1.31	**<0.001**	2.47 ± 0.75	3.72 ± 0.44	**<0.001**
– Warming II	2.27 ± 0.64	3.81 ± 0.56	0.12	3.06 ± 0.78	3.35 ± 1.39	**<0.001**	2.80 ± 0.79	4.06 ± 0.45	**<0.001**
Preoperative Hb, g(%)	18.23 ± 4.35	12.28 ± 1.08	**<0.001**	17.22 ± 2.40	11.84 ± 0.70	**<0.001**	18.53 ± 2.51	11.99 ± 0.45	**<0.001**
SaO_2 (%)	82.33 ± 7.23	94.55 ± 3.44	**<0.001**	87.23 ± 4.02	96.32 ± 2.63	**0.007**	88.0 ± 5.68	97.18 ± 1.77	**<0.001**
Internal jugular venous oxygen saturation (%)									
– Pre-bypass	64.91 ± 5.60	74.17 ± 6.56	0.33	67.64 ± 7.34	72.09 ± 10.09	0.64	72.76 ± 38.17	71.88 ± 9.10	0.56
– Cooling I	–	–	–	70.43 ± 4.55	74.92 ± 8.41	**<0.001**	74.58 ± 6.80	73.10 ± 7.61	0.89
– Cooling II	–	–	–	72.13 ± 5.03	75.90 ± 10.60	**0.005**	82.27 ± 54.00	74.51 ± 7.73	0.64
– Warming I	58.0 ± 4.24	65.50 ± 8.39	**<0.001**	57.27 ± 10.63	62.38 ± 7.91	0.38	64.32 ± 9.11	59.86 ± 7.96	**0.02**
– Warming II	78.60 ± 6.69	77.95 ± 5.66	0.19	77.30 ± 4.72	76.18 ± 9.96	**0.027**	78.69 ± 7.18	77.07 ± 8.58	0.14
– Post-bypass	73.93 ± 6.27	76.60 ± 4.33	**0.009**	74.29 ± 4.65	75.16 ± 5.95	0.24	76.87 ± 4.71	73.90 ± 6.68	0.002
Cerebral (a-v)O_2 saturation (%)									
– Pre-bypass	18.26 ± 6.99	20.39 ± 7.52	0.80	19.58 ± 7.28	24.23 ± 10.22	0.68	15.24 ± 38.50	25.29 ± 9.92	0.58
– Cooling	–	–	–	16.80 ± 6.32	21.40 ± 9.36	**0.007**	13.42 ± 8.65	24.08 ± 7.81	0.16
– Warming I	24.51 ± 5.59	29.06 ± 9.36	**<0.001**	29.96 ± 12.76	33.94 ± 9.09	0.42	23.68 ± 11.64	37.3 ± 8.21	**<0.001**
– Warming II	8.19 ± 7.17	16.6 ± 7.38	0.79	9.93 ± 5.79	20.14 ± 10.78	**0.04**	9.31 ± 10.36	20.10 ± 9.12	0.45
– Post-bypass	9.98 ± 8.0	17.95 ± 5.88	**0.003**	12.94 ± 6.11	21.16 ± 6.38	0.57	11.13 ± 7.42	23.28 ± 7.27	0.67

Table 6. Pairwise comparisons of perfusion flow rate, internal jugular venous oxygen saturation and cerebral arteriovenous oxygen saturation difference by *post hoc* analysis (n=548).

Groups of patients	Perfusion flow rate ($L.min^{-1}.m^2$)			
(p-value)	Initiation of cooling	Stable cooling	Initiation of re-warming	Stable re-warming
I vs. II	–	–	NS	NS
I vs. III	–	–	0.004	0.01
II vs. III	NS	NS	NS	NS
	Internal jugular venous oxygen saturation (%)			
I vs. II	–	–	NS	0.02
I vs. III	–	–	0.02	NS
II vs. III	NS	NS	NS	NS
	Cerebral arteriovenous oxygen saturation difference			
I vs. II	NS	NS	<0.001	NS
I vs. III	NS	NS	NS	NS
II vs. III	0.04	0.04	<0.001	0.008

NS – non-significant

sons, the normothermic CPB group and the cyanotics exhibited greater cerebral desaturation, increased cerebral arteriovenous oxygen saturation difference, and required a greater amount of perfusion flow than the hypothermic CPB group. It is noteworthy that the acyanotic subset of patients of the normothermic group exhibited greater cerebral arteriovenous oxygen saturation difference as compared to cyanotics in the postoperative period (p=0.003) (Table 5).

Interrelationship of jugular venous desaturation, increased cerebral arteriovenous oxygen saturation difference and neurological dysfunction following normothermic and hypothermic CPB in cyanotics and acyanotics

According to reports in the literature, the management of arterial pH and PCO_2 during CPB remains controversial. There is general agreement that a pH stat strategy is probably beneficial in children, where increased cerebral blood flow (CFB) does increase the rate of cooling and thus increases the chance of uniform cerebral hypothermia.[1-3,9] In contrast, in adults, an alpha stat strategy may provide the greatest cerebral protection during hypothermia on CPB.[13,14]

This study group was comprised of a heterogeneous cohort of symptomatic patients with diverse anatomical diagnoses who required different temperature management protocols for surgical correction. pH stat strategy was employed only for patients with cyanotic congenital heart diseases undergoing corrective cardiac surgery under deep hypothermia. The depth of anaesthesia was uniform in all patients of the study group. There was no effect of pH stat or alpha stat strategy on cerebral oxygenation in this study group. It is noteworthy that 6 of the 20 patients who died perioperatively in this study group had global cerebral ischaemic insults, while $IJVO_2$ in all of them was between 60-75% at normothermia. There were no reversible or irreversible cerebral ischaemic insults in any patient with $IJVO_2$ >75%.

This study further demonstrated that 64.5% and 59.8% of patients undergoing normothermic and hypothermic CPB, respectively, adapted to increased perfusion flow. The degree of cerebral oxygen desaturation decreased and mean $IJVO_2$ saturation tended to increase throughout bypass. If we presume that the cerebral metabolic rate for oxygen is constant during normothermic CPB, as was mean arterial pressure, an increase in cerebral venous saturation could be explained by microcirculatory adjustments to increased pump flow. This circulatory change appears to be sustained after CPB, as demonstrated by persistent elevations of $IJVO_2$ in the post-bypass periods.

Hypothermia reduces cerebral metabolic oxygen consumption to a proportionately greater extent that cerebral blood flow, resulting in "luxuriant perfusion".[9,14,15] The increase in internal jugular venous oxygen saturation and decreased cerebral oxygen extraction in this study provide further physiological evidence for this phenomenon. We concur with the observations of other investigators who demonstrated similar changes in near-infrared spectroscopy, jugular bulb haemoglobin-oxygen saturation or CBF/cerebral metabolic rate for oxygen during CPB cooling.[9,13,16] Furthermore, jugular venous desaturation and increased cerebral oxygen extraction during the re-warming phase of CPB indicates inadequate CBF in proportion to oxygen consumption and greater oxygen extraction during hypothermia.[9]

Although the prevalence of cerebral air embolism may not be affected by brain temperature, it has been shown to cause more damage in the warm brain through the formation of energy-dependent pinocytic vesicles and transendothelial channels involving mainly the neocortex, periventricular white matter and basal ganglia.[17,18]

Overall, our results show that CPB methods differing in temperature or pump flow can result in different cerebral oxygen supply-demand relationships during bypass in both cyanotics and acyanotics and may be the causative factors for a suboptimal neurological outcome following cardiopulmonary bypass.

Study limitations

The major limitation of our study was non-randomisation. Given the significant heterogeneity of clinical characteristics, the small number of patients in each subgroup and the requirement of wide range of individualised surgical procedures for each patient, a prospective randomised controlled trial was considered unethical.

Secondly, both children and adults, with a multitude of diagnoses and operations, were included in this study. The baseline characteristics of the patients were markedly varied. Thirdly, this study excluded the group of patients who are at high risk for neurological events. Fourthly, cerebral venous oxygen saturation assesses the balance between CBF and cerebral metabolic rate for oxygen ($CMRO_2$), but does not quantify either variable. Therefore, specific measurements of CBF and $CMRO_2$ during CPB would be more desirable. And

finally, because internal jugular venous oxygen saturation is a global assessment, cerebral oxygen saturation may be insensitive to focal ischaemic events.

A comprehensive project to directly quantify cerebral blood flow and metabolism, combined with intraoperative electroencephalography, and an analysis of their relationship to perfusion flow rates at different nasopharyngeal temperatures together with a postoperative neuropsychological assessment, is in progress and aims to answer many unresolved questions.

Conclusions

We conclude that patients undergoing normothermic CPB are at greater (higher observed incidence) risk of cerebral venous desaturation than patients undergoing hypothermic CPB, irrespective of age. Cyanotics revealed a greater extent of desaturation as compared to acyanotics during normothermic CPB and during the re-warming phase of hypothermic CPB.

There is evidence of the occurrence of a cerebral blood flow-metabolism imbalance during and after warming from hypothermic CPB in a significant percentage of patients undergoing open-heart surgery, indicating that an individualised increased perfusion flow requirement is mandatory. We recommend routine monitoring of internal jugular venous oxygen saturation in all patients undergoing open-heart surgery under CPB.

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