Mortality after neonatal cardiac surgery: Prediction from mean arterial pressure after rewarming in the operating room

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Objective: To examine the predictive contribution of mean arterial pressure after rewarming to $\geq 34^{\circ}\text{C}$ in the operating room to mortality after cardiac surgery in infants ≤ 6 weeks old.

Methods: In this prospective inception cohort study, 70 consecutive infants who had open cardiac surgery with deep hypothermic circulatory arrest when ≤ 6 weeks old in the years 1996 to 1999 had follow-up to 5 years of age. Demographic, preoperative, operative, and postoperative variables were recorded prospectively. The previously unexplored variables of lowest mean arterial pressure in the operating room after rewarming to 34°C were recorded retrospectively from anesthesia records. Predictor variables for death were examined using univariate and multivariate analyses.

Results: Deep hypothermic circulatory arrest time, re-cardiopulmonary bypass in the operating room, duration of mean arterial pressure below 40, 35, 30, and 25 mm Hg after rewarming in the operating room, time for lactate to return to ≤ 2 mmol/L postoperatively, and cardiopulmonary resuscitation were significantly associated with death at 1 and 5 years of age on univariate analysis. Multivariate stepwise forward logistic regression analysis found the duration of mean arterial pressure after rewarming below 30 mm Hg (odds ratio 1.094; 95% confidence interval 1.033–1.158) and cardiopulmonary resuscitation (odds ratio 13.800, 95% CI 3.062–62.194) were significant predictors of death by 5 years of age. Stepwise multiple regression using pre- and intraoperative variables accounted for 30.1% of the variability related to mean arterial pressure ≤ 30 mm Hg after rewarming.

Conclusion: In these infants, low mean arterial pressure after rewarming in the operating room, even for brief times, is significantly associated with death.

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There is a growing literature describing the outcomes of infants receiving open cardiac surgery in early infancy.¹⁻³ Mortality has been reduced but still remains significant, particularly in patients with some complex lesions such as hypoplastic left heart syndrome.¹ Several studies have been published regarding predictors of outcomes after congenital heart disease surgery.⁴⁻⁷ Most studies find the cause of adverse outcome to be multifactorial, including preoperative, intraoperative, and postoperative conditions and events.¹⁻⁸

Many variables that have been found to predict outcome after surgery for congenital heart disease are not modifiable. Examples include type of lesion, preoperative neurologic examination, preoperative microcephaly, chromosomal anomalies, and socioeconomic status.¹⁻⁷ Also, many postoperative variables such as severity of illness and duration of intensive care may not be modifiable and may be heavily influenced by events and conditions present prior to and during surgery. The mean arterial pressure (MAP) in the operating room (OR) after rewarming to a

Abbreviations and Acronyms

CPB	= cardiopulmonary bypass
DHCA	= deep hypothermic circulatory arrest
HLHS	= hypoplastic left heart syndrome
MAP	= mean arterial pressure
OR	= operating room
PRISM	= pediatric risk of mortality

temperature of $\geq 34^{\circ}\text{C}$, while on or off of cardiopulmonary bypass (CPB), is a potentially modifiable variable. The MAP is a surrogate for the perfusion pressure supplying blood flow to the tissues^{9,10} and may be particularly relevant on rewarming when metabolism is “reactivated.”⁸

The objective of this study was to examine the predictive contribution to mortality of the potentially modifiable variable of MAP after rewarming in the OR after open cardiac surgery in infants 6 weeks old or less.

Materials and Methods**Design**

This prospective descriptive study is part of a larger interprovincial inception cohort study established to examine outcomes of infants ≤ 6 weeks of age who receive complex, open cardiac surgery. Ethics Boards approvals were obtained prior to onset of the study, and all patients’ parents/guardians signed informed consent forms.

Subjects

The subjects all had complex intracardiac surgery done at ≤ 6 weeks of age using CPB and deep hypothermic circulatory arrest (DHCA) at the Stollery Children’s Hospital, Edmonton, Alberta, through the Western Canadian Children’s Heart Network. No child was excluded for any reason.

Procedure

All infants were enrolled by a nurse research assistant. Clinical and laboratory parameters that had been agreed upon prior to data collection were recorded prospectively; these are described elsewhere¹¹ and listed in the results (see Table 2). A new intraoperative variable, the MAP after rewarming to a core temperature of at least 34°C in the OR (on or off of CPB and before transfer to pediatric intensive care) was obtained by one of the authors (A.J.) by retrospective review of the anesthesia record for each patient and blinded to outcome. Blood pressure was monitored continuously via arterial line in the operating room and recorded by hand by the anesthetist at 5-minute intervals onto the anesthesia record. This variable was recorded as the duration of MAP below specific thresholds (40, 35, 30, 25, and 20 mm Hg) in the operating room after rewarming. Follow-up assessments were scheduled at the Neonatal Follow-up Clinics at the tertiary site of origin in the various provinces. All patients had follow-up data for the primary outcome of mortality during hospitalization, at 1 year, and at 5 years of age.

During the time of this study, there was no protocol for anesthetic management or blood pressure management in the operating

TABLE 1. Primary cardiac diagnoses and surgery for the cohort of 70 infants ≤ 6 weeks of age

Cardiac diagnosis (surgical procedure)	Number
Hypoplastic left heart syndrome (Norwood procedure)	26
Transposition of the great arteries $\pm$ ventricular septal defect (arterial switch procedure)	14
Simple total anomalous pulmonary venous connection (repair)	6
Miscellaneous lesions (repair)	24
Truncus arteriosus	6
Hypoplastic aortic arch (2 with single-ventricle anatomy)	7
Interrupted aortic arch (1 with single-ventricle anatomy)	5
Complex anomalies involving the great arteries or mitral valve (2 with single-ventricle anatomy)	6

room. These were left to the discretion of the anesthetist. This “natural variability” in management was important for the observational design of this study. In general, maintenance anesthesia during CPB was with high-dose opioid using fentanyl or sufentanil and supplemented by volatile anesthetic including sevoflurane, desflurane, or isoflurane at the anesthetist’s discretion. When inotropes were deemed necessary, dopamine was started, and if not sufficient at a dose of $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, an epinephrine infusion was added. Phenoxybenzamine was not used in these patients, and amrinone or milrinone usage was rare in the operating room.

Statistics

All data were transferred for entry to The Registry and Follow-up of Complex Pediatric Therapies Project at the Glenrose Rehabilitation Hospital, Edmonton, Alberta. Univariate analyses for death were done using *t* tests for equality of means preceded by Levene’s test for equality of variances, χ^2 test with Yates correction or Fisher exact test (2 sided) when appropriate. Pearson product moment correlations among variables were done with 2-tailed significance. Bonferroni correction for multiple tests was applied in all cases. Multivariate stepwise forward logistic regression was used to develop prognostic indicators of death from the preoperative, intraoperative, and postoperative periods using the Wald statistic, at a significance level of .05. Stepwise multiple regression using preoperative and operative variables was used to predict the MAP after rewarming variables. SPSS (SPSS, Chicago, Ill), version 12.0 for Windows was used for analysis. The funding agency had no role in data collection, analysis, interpretation, or manuscript approval.

Results

Seventy consecutive subjects from September 1996 through August 1999 were identified at the time of open cardiac surgery. The primary cardiac diagnoses and surgery are shown in Table 1. Survival outcome is available for all patients. There were 51 survivors (73%): 13 deaths occurred during the initial hospitalization (19%), 2 more by 1 year of

TABLE 2. Demographic, preoperative, operative, and postoperative characteristics of the 70 infants of ≤6 weeks of age with complex intracardiac surgery in relation to death at or before 5 years of age

Demographics/preoperative/operative variables	Total (n = 70)	Survival (n = 51)	Death (n = 19)	χ^2 , <i>t</i> , exact tests*	<i>P</i>
Gender (male)	43 (61%)	32 (63%)	11 (58%)	.137	.711
Birth gestation (wk)	39 (2)	39 (2)	39 (1)	.783	.437
Birth weight (kg)	3.3 (.6)	3.3 (.6)	3.2 (.5)	.648	.519
Birth head circumference (cm)	34 (2)	34 (1)	34 (2)	.525	.605
Apgar (5 min)	8 (1)	8 (1)	8 (.5)	—	.999
Chromosomal abnormality	9 (13%)	7 (14%)	2 (11%)	.126	.722
Age at surgery (d)	12.5 (20)	13 (23)	12 (11)	.155	.877
Single ventricle anatomy	30 (43%)	17 (33%)	13 (68%)	6.959	.008
HLHS	26 (37%)	15 (29%)	11 (60%)	—	.05
TGA	14 (20%)	14 (28%)	0 (0%)	—	.008
STAPVC	6 (9%)	6 (12%)	0 (0%)	—	.180
MISC	24 (34%)	16 (31%)	8 (42%)	—	.412
Cardiopulmonary bypass time (min)	105 (54)	92 (36)	140 (77)	−2.585	.017
Lowest MAP for ≥10 min on CPB	20 (14)	22 (16)	17 (7)	1.187	.239
Lowest flow for ≥10 minute during CPB (mL · kg ^{−1} · min ^{−1})	100 (24)	99 (27)	101 (18)	−.300	.765
Lowest temperature (°C) for ≥10 min during CPB	24.0 (3.2)	23.0 (3.4)	24.1 (2.9)	−.282	.779
Blood temperature immediately prior to DHCA	20.5 (2.2)	20.6 (3.3)	20.1 (3.1)	.609	.545
Crossclamp time (min)	56 (21)	52 (20)	68 (21)	−2.953	.004
DHCA time (min)	41 (22)	36 (21)	54 (18)	−3.479	.001
Re-CPB in OR	19 (27%)	8 (16%)	11 (58%)	12.471	<.001
Day 1 postoperative variables	n = 68	n = 51	n = 17	<i>t</i> or χ^2	
Highest dopamine on day 1	10 (5)	10 (1)	11 (2)	−.657	.519
Highest plasma lactate, day 1	8 (6)	7 (4)	12 (18)	−2.814	.011
Time for plasma lactate to return to ≤2	16 (10)	14 (10)	23 (10)	−.3693	<.001
Time for plasma lactate to return to ≤5	5 (7)	4 (5)	10 (10)	−2.652	.016
Lowest arterial pH	7.33 (.09)	7.35 (.08)	7.27 (.12)	3.035	.003
Lowest base deficit	.18 (7)	.55 (4)	−.91 (13)	.441	.665
Day 2-5 postoperative variables	n = 66	n = 51	n = 15	<i>t</i> or χ^2	
Highest dopamine	10 (6)	8 (4)	14 (8)	−2532	.022
Highest plasma lactate	5 (6)	3 (3)	10 (9)	−2.977	.010
Variables from any time period					
Seizures	9 (13%)	6 (12%)	3 (6%)	—	.696
Cardiopulmonary resuscitation given	16 (23%)	5 (10%)	11 (58%)	—	<.001
Extracorporeal membrane oxygenation	4 (6%)	0 (0%)	4 (21%)	—	.004
Days of ventilation	14 (15)	12 (12)	19 (21)	−1.405	.174
Days of hospitalization	31 (26)	31 (25)	32 (27)	−.179	.859
Lowest hemoglobin in the first 5 d postoperatively	111 (16)	110 (15)	112 (20)	−.336	.738

Data given as mean (SD) or n (%).

**t* test for equality of means preceded by Levene's test for equality of variances; χ^2 with Yates correction, or Fisher exact test (2-sided) when appropriate. After Bonferroni correction for multiple analyses, *P* values of <.002 remain significant. *CPB*, Cardiopulmonary bypass; *DHCA*, deep hypothermic circulatory arrest; *HLHS*, hypoplastic left heart syndrome; *MAP*, mean arterial pressure, mm Hg; *MISC*, miscellaneous cardiac lesions; *STAPVC*, simple total anomalous pulmonary venous connection; *TGA*, transposition of the great arteries.

age (21%), and 4 more by 5 years of age (27%). More details of the findings in this cohort of patients have been published.¹¹

Univariate Analyses

Potential predictors of death at age 5 years available for all 70 subjects and considered in the univariate analysis are shown in Table 2. The variables concerning MAP after

rewarming to 34°C in the operating room and their relation to mortality during hospitalization and at 1 and 5 years of age are shown in Table 3.

Multivariate Analyses

All variables that predicted death in the univariate analyses with a *P* < .002 (DHCA time, re-CPB in the OR, MAP after rewarming in the OR, time for plasma lactate to return to

TABLE 3. Duration of mean arterial pressure below the thresholds after rewarming to at least 34°C in the operating room in relation to death at 1 and 5 years of age for 70 infants after complex intracardiac surgery done at ≤6 weeks of age

Outcome period	Outcome at initial hospitalization			<i>T</i> *	<i>P</i>
	Total*	Survival	Death		
Outcome at initial hospitalization	n = 70	n = 57	n = 12		
Duration (min) of MAP below a threshold of:					
40 mm Hg	19 (12)	17 (12)	25 (10)	−2.428	.024
35 mm Hg	14 (13)	11 (12)	23 (11)	−3.185	.002
30 mm Hg	10 (12)	8 (11)	19 (12)	−3.318	.001
25 mm Hg	5 (10)	3 (8)	13 (14)	−2.744	.016
20 mm Hg	3 (7)	2 (6)	6 (9)	−1.543	.144
Outcome at 1 year of age	n = 70	n = 55	n = 15		
Duration (min) of MAP below a threshold of:					
40 mm Hg	19 (12)	17 (12)	26 (9)	−3.039	.005
35 mm Hg	14 (13)	11 (12)	24 (10)	−4.237	<.001
30 mm Hg	10 (12)	7 (11)	21 (12)	−4.123	.001
25 mm Hg	5 (10)	2 (6)	16 (14)	−3.796	.002
20 mm Hg	3 (7)	1 (5)	7 (11)	−2.037	.059
Outcome at 5 years of age	n = 70	n = 51	n = 19		
Duration (min) of MAP below a threshold of:					
40 mm Hg	19 (12)	16 (12)	25 (8)	−3.422	.001
35 mm Hg	14 (13)	11 (12)	22 (11)	−3.465	.001
30 mm Hg	10 (12)	6 (11)	19 (12)	−4.149	<.001
25 mm Hg	5 (10)	2 (6)	12 (14)	−3.149	.005
20 mm Hg	3 (7)	2 (5)	6 (14)	−1.741	.096

*Data given as minutes (SD). *t* test for equality of means preceded by Levene's test for equality of variances. After Bonferonni correction for multiple analyses, *P* values of ≤.005 remain significant. MAP, Mean arterial pressure after rewarming to ≥34°C in the operating room.

≤2 mmol/L postoperatively, and CPR) or that were considered potentially clinically important (single-ventricle anatomy, hypoplastic left heart syndrome [HLHS], transposition of the great arteries, aortic crossclamp time, lowest arterial pH day 1 postoperatively, and use of extracorporeal membrane oxygenation) were entered in a stepwise forward logistic regression. The results for predicting death at initial hospital discharge, 1 year of age, and 5 years of age are

shown in Table 4. The MAP after rewarming in the OR was the only potentially modifiable variable to be associated with mortality.

MAP on Rewarming

The significant correlations of the MAP after rewarming in the OR with selected pre- and intraoperative variables is shown in Table 5. No significant correlation of the

TABLE 4. Multivariate stepwise forward logistic regression of significant predictor variables* for death in 70 infants of ≤6 weeks of age with complex intracardiac surgery

Model	Variables	B	SE	Wald	Sign	Odds ratio	95% CI
A. Death by hospital discharge	Duration of MAP ≤30 mm Hg (min)	.106	.046	5.342	.021	1.112	1.016–1.216
	CPR	4.508	1.162	15.036	<0.001	90.700	9.292–885.311
B. Death by 1 year of age	Duration of MAP ≤25 mm Hg (min)	.144	.045	10.254	.001	1.155	1.058–1.262
	CPR	3.844	1.066	13.009	.000	46.720	5.785–377.313
C. Death by 5 years of age	Duration of MAP ≤30 mm Hg (min)	.090	.029	9.418	.002	1.094	1.033–1.158
	CPR	2.625	.768	11.674	.001	13.800	3.062–62.194

*The variables entered included: single-ventricle anatomy, hypoplastic left heart syndrome, transposition of the great arteries, aortic crossclamp time, deep hypothermic circulatory arrest time, re-cardiopulmonary bypass in the operating room, time for plasma lactate to return to ≤2 mmol/L on the day postoperative, lowest arterial pH on the day postoperative, CPR given at any time, extracorporeal membrane oxygenation, and duration (minutes) of MAP after rewarming to 34°C in the operating room below thresholds of 40, 35, 30, and 25 mm Hg. CPR, cardiopulmonary resuscitation; MAP, mean arterial pressure.

TABLE 5. Significant correlations with duration of mean arterial pressure after rewarming in the operating room for 70 infants after complex intracardiac surgery done at ≤6 weeks of age

Variable	Duration MAP ≤30 mm Hg	Duration MAP ≤25 mm Hg
HLHS	$r = .271, P = .024$	$r = .206, P = .088$
TGA	$r = -.201, P = .096$	NS
CPB time	$r = .482, P < .001$	$r = .578, P < .001$
Crossclamp time	$r = .206, P = .087$	$r = .272, P = .023$
DHCA time	$r = .335, P = .003$	$r = .407, P < .001$
Repeat CPB in operating room	$r = .529, P < .001$	$r = .550, P < .001$

Variables with $P > .10$ include: birth weight, gestational age, single-ventricle anatomy, highest dopamine dose preoperatively, highest lactate preoperatively, days of ventilation preoperatively, and lowest flow on CPB. After Bonferroni correction for multiple analyses, P values of $\leq .004$ remain significant. There were $n = 70$ for preoperative variables, $n = 68$ for day 1 variables, and $n = 66$ for day 2–5 variables. *CPB*, Cardiopulmonary bypass; *DHCA*, deep hypothermic circulatory arrest; *HLHS*, hypoplastic left heart syndrome; *MAP*, mean arterial pressure after rewarming to 34°C in the operating room; *TGA*, transposition of the great arteries.

MAP after rewarming in the OR was found with birth weight, gestational age, single-ventricle anatomy, highest dopamine dose preoperatively, highest plasma lactate preoperatively, days of ventilation preoperatively, or lowest flow on CPB. The variables from preoperative and operative periods that had a correlation with a $P \leq .1$ (Table 5) were entered into a stepwise multiple regression to predict the MAP after rewarming in the OR. The multiple regression accounted for 30.1% of the variability for MAP ≤ 30 mm Hg and 38.4% of the variability for MAP ≤ 25 mm Hg (Table 6). Finally, duration of MAP ≤ 30 mm Hg and ≤ 25 mm Hg after rewarming in the OR showed no correlation with the time for plasma lactate to return to ≤5 mmol/L day 1 postoperatively, time for plasma lactate to return to ≤2 mmol/L day 1 postoperatively, highest dopamine dose day 1 postoperatively, highest epinephrine dose day 1 postoperatively, or high-

est plasma lactate day 2 postoperatively. There was a significant correlation with the highest plasma lactate on postoperative day 1: for duration of MAP ≤ 35 mm Hg ($r = .366, P = .002$) and for duration of MAP ≤ 25 mm Hg ($r = .316, P = .009$).

The lowest values of MAP after rewarming in the OR were examined more closely to determine their timing in relation to CPB. The lowest values occurred while on CPB in 35%, while off CPB in 54%, and overlapping both times in 12%. The period on CPB after rewarming to 34°C accounted for 73% and 93% of the MAP values less than 30 mm Hg and 25 mm Hg, respectively.

Discussion

In this observational study, many variables were examined to determine their relation to mortality after complex open cardiac surgery in infants ≤6 weeks old. The study took advantage of the variability in clinical management of MAP in the OR to examine the predictive potential of this variable. The main finding of this study is that a low MAP after rewarming in the OR is a significant predictor of death at 5 years of age in both univariate and multivariate stepwise forward logistic regression analyses. Furthermore, only 30% to 38% of the variance related to MAP on rewarming in the OR could be accounted for in stepwise multiple regressions. To our knowledge, MAP after rewarming in the OR has not been previously examined in predicting outcomes after congenital heart disease surgery. Our data suggest that a MAP after rewarming in the OR of ≥35 mm Hg is desirable and that a MAP below this may be detrimental, even for brief periods of time.

There are theoretical reasons to suggest that a low MAP immediately after rewarming may be a direct cause of poor outcome. The goal in treatment of shock is to maintain perfusion pressure above the critical point below which blood flow cannot be effectively maintained in individual organs.^{9,10} Below a certain threshold there will be inadequate organ and tissue perfusion, and cellular

TABLE 6. Stepwise multiple regressions to predict mean arterial pressure after rewarming to 34°C in the operating room of 70 infants after complex intracardiac surgery done at ≤6 weeks of age

Model	Variable	Adj r^2	Slope	Standard error	T	P
A. Duration of MAP ≤30 mm Hg after rewarming (min)	Need for re-CPB in OR	.269	7.302	3.630	2.012	.048
	CPB time	.301	.074	.029	2.582	.012
	HLHS	.334	5.560	2.663	2.088	.041
	CPB time	.324	.093	.018	5.148	<.001
B. Duration of MAP ≤ 25 mm Hg after rewarming (min)	DHCA time	.384	.123	.045	.271	.007

Variables used included HLHS, TGA, CPB time, crossclamp time, DHCA time, and need for re-CPB in operating room. *CPB*, Cardiopulmonary bypass; *DHCA*, deep hypothermic circulatory arrest; *HLHS*, hypoplastic left heart syndrome; *MAP*, mean arterial pressure on rewarming to 34°C in the operating room; *OR*, operating room; *TGA*, transposition of the great arteries.

injury. This threshold may be especially important after cardiac surgery in infants in view of their significant systemic inflammatory response to CPB,^{12,13} making the microcirculation particularly vulnerable to an inadequate perfusion pressure.¹⁴ There is altered regulation of microvascular tone,^{8,14} plugging of the microcirculation due to microthrombi and cellular adhesion events,^{8,14} and a heterogeneous alteration of capillary density and perfusion.¹⁵ In this study, the period of low MAP after rewarming included time on CPB when it can be argued that there is normal systemic blood flow, regardless of the patient MAP. The period on CPB after rewarming to 34°C accounted for 73% and 93% of the MAP values less than 30 mm Hg and 25 mm Hg, respectively. This suggests that it is not simply systemic blood flow that is important; rather, it may be perfusion pressure to the microcirculation of the tissues that is critical.

There is clinical evidence to support this theoretical argument for a direct adverse effect on survival of a low MAP. In the pediatric risk of mortality (PRISM) score, the low systolic blood pressure limits for predicting stepwise increased mortality rates in infants were <55 mm Hg and <40 mm Hg.¹⁶ This was also the case for neonates in the more recent PRISM III score.¹⁷ In the pediatric logistic organ dysfunction score, the low systolic blood pressure limits to assign stepwise increased cardiovascular organ dysfunction in term neonates are <65 mm Hg and <35 mm Hg.¹⁸ Recent consensus guidelines on management of sepsis in adults suggest that a MAP $\geq$ 60 mm Hg is needed to achieve adequate tissue blood flow.¹⁰ Similar consensus guidelines in pediatrics have recommended that the perfusion pressure (MAP minus central venous pressure) be kept $\geq$ 55 mm Hg in term newborns to maintain organ blood flow.⁹ Early phases of inflammatory processes may be a particularly vulnerable time. When supraphysiologic goals of resuscitation are used in established critical illness, there is no effect on outcome¹⁹; however, when they are used early in severe sepsis²⁰ or high-risk surgical patients,²¹ there is significant improvement in mortality and organ dysfunction. Comprehensive early therapy may limit the progression of the cascades leading to multiple organ dysfunction and death.¹⁹

The current study supports the theory that a low MAP may lead to tissue hypoxia, an exaggerated inflammatory response, multiple organ dysfunction, and death. The MAP variables on rewarming were significantly predictive of mortality in stepwise forward logistic regressions that included factors from all time periods of hospitalization. In addition, using many variables from the pre- and intraoperative time periods in a stepwise multiple regression could only explain <40% of the variability related to MAP after rewarming, suggesting that most of

the predictive ability of MAP on rewarming was not due to another interrelated variable. The MAP on rewarming correlated with the lactate on the first postoperative day. This suggests that the MAP was a valid surrogate for tissue perfusion and that a threshold of perfusion had been crossed, resulting in tissue hypoxia and anaerobic metabolism. The lack of correlation to dopamine dose or epinephrine dose or the time for lactate to return to $\leq$ 5 mmol/L or $\leq$ 2 mmol/L on the first postoperative day suggests this was not due to ongoing myocardial dysfunction. It is possible that the low MAP led to the ultimate development of “cytopathic hypoxia,” leading to organ dysfunction and death.^{19,22} Indeed, death was associated with multiple organ dysfunction syndrome in 10/13 (77%) of the deaths during initial hospitalization, rather than sudden death. It is also plausible that initial “cytopathic hypoxia” may have caused permanent microvascular or cellular injury that resulted in the late deaths up to 5 years of age associated with subsequent illness or surgery. This hypothesis merits further investigation, as we are aware of no data to confirm or refute this possibility.

Some authors have described excellent outcomes after the Norwood procedure using phenoxybenzamine and milrinone in the operating room to lower systemic vascular resistance.²³⁻²⁵ In these studies, the MAP in the first 48 hours postoperatively ranged from 44 to 62 mm Hg²³⁻²⁵ and thus was much higher than that predicting mortality in the current study. In those studies epinephrine and norepinephrine were used to maintain a MAP greater than 45 mm Hg on separation from CPB.²³⁻²⁵ The results of these studies suggest that vasodilation is not in itself deleterious as long as MAP is maintained in a reasonable range.

These results apply to a very select patient population, those who had neonatal cardiac surgery requiring DHCA during the period 1996 to 1999, and include a large number of HLHS and other complex lesions. The 30-day postoperative mortality during this period for this complex group of neonates was 10/70 (14.3%). Whether the results still apply in the current era of neonatal cardiac surgery cannot be proven with these data. From 2001 to 2004, our 30-day mortality for complex neonatal open cardiac surgery was 8/170 (4.7%); 30-day mortality for cardiac surgery in those <17 years was 24/2072 (1.2%).

There are limitations to this study. This was not a randomized trial and therefore the associations shown cannot be definitively identified as cause and effect. The study included a relatively small and heterogeneous group of patients having neonatal cardiac surgery and therefore there may be unaccounted for differences between patients that confound the interpretation of the results. Many of the variables were highly correlated and

therefore the low MAP may be a manifestation of other underlying etiologic factors, in and of itself not harmful. For example, some specific variables such as anesthetic management and OR inotrope use were not protocolized and not recorded for this study and may confound the interpretation of why low MAP is associated with mortality. The exact cause of the low MAP in this study could not be ascertained. Theoretically, it could be due to low systemic vascular resistance, low cardiac output, or both. That most of the low MAP values occurred while on CPB may suggest that a low MAP was predominately due to low systemic vascular resistance; however, this is not certain because we were unable to record the flow on CPB after rewarming in the operating room. We were also unable to determine what therapeutic interventions were attempted for a low MAP in the operating room. Given this, we cannot determine the best therapeutic option when faced with a low MAP. Nevertheless, this observational study suggests that a novel parameter, the MAP after rewarming in the operating room, is associated with outcome and warrants further investigation.

In view of these limitations, one could argue that the MAP on rewarming variables are associated with outcome simply because they are a marker for worse cardiac function postoperatively. Whether intervention to increase the MAP will improve outcome or have its own complications can only be answered by further study.

Conclusions

Despite these limitations, the main finding of the significant association of MAP after rewarming in the OR and death during hospitalization, at 1 year, and at 5 years of age is we believe, biologically plausible and likely causative. We recommend caution in accepting a low MAP in these infants after rewarming in the OR. We suggest that the time after rewarming may be a vulnerable period for the tissue microcirculation, and for this reason, the low MAP on reactivation of metabolism with rewarming may be a causative factor contributing to outcome. This observation is a novel finding, is hypothesis generating, and should lead to further investigation.

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