The effect of hematocrit during hypothermic cardiopulmonary bypass in infant heart surgery: Results from the combined Boston hematocrit trials

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Registered with clinicaltrials.gov (#) NCT00006183.

Supported by grants HL 063411 and RR 02172 from the National Institutes of Health and by the Farb Family Fund.

Received for publication Jan 9, 2007; revisions received Feb 9, 2007; accepted for publication March 6, 2007.

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J Thorac Cardiovasc Surg 2008;135:355-60
0022-5223/\$34.00

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doi:10.1016/j.jtcvs.2007.03.067

Objective: Two randomized trials of hematocrit strategy during hypothermic cardiopulmonary bypass in infant heart surgery have been performed. The first suggested worse outcomes were concentrated in patients with lower hematocrit levels (approximately 20%), whereas the second suggested there was little benefit to increasing the hematocrit level above 25%. The form of the relationship between continuous hematocrit levels and outcomes requires further study.

Methods: In the two trials, 271 infants who underwent biventricular repair not involving the aortic arch were enrolled. Analysis was undertaken of the effects of hematocrit level, as a continuous variable, at the onset of low-flow cardiopulmonary bypass.

Results: Psychomotor Development Index scores at age 1 year varied nonlinearly with hematocrit levels, with increasing scores up to 23.5% hematocrit ($P < .001$) and a plateau effect beyond 23.5% ($P = .42$), based on a piecewise linear model. Lower hematocrit levels were associated with more positive intraoperative fluid balance ($P < .001$ for linear trend) and marginally associated with higher serum lactate levels at 60 minutes after bypass ($P = .08$ for linear trend), but not with blood products given, nadir of cardiac index in the first 24 hours, or Mental Development Index scores.

Conclusions: A hematocrit level at the onset of low-flow cardiopulmonary bypass of approximately 24% or higher is associated with higher Psychomotor Development Index scores and reduced lactate levels. Because the effects of hemodilution may vary according to diagnosis, age at operation, bypass variables such as pH strategy and flow rate, and other perioperative factors, this study cannot ascertain a universally "safe" hemodilution level.

Hemodilution during hypothermic cardiopulmonary bypass (CPB) was used initially in the 1950s, with the rationale that it would reduce the use of blood and blood products,¹ as well as improve perfusion in microvessels.² Subsequently, concerns emerged about potential adverse effects of hemodilution, including reduced perfusion pressure, increased cerebral blood flow and hence increased risk for cerebral microemboli, and decreased oxygen-carrying capacity.³⁻⁵

We⁶ previously conducted a randomized trial of 147 patients, of whom 74 were assigned to a lower-hematocrit strategy at onset of low-flow CPB ($21.5\% \pm 2.9\%$, mean $\pm$ SD, with a target of 20%) and 73 to a higher-hematocrit strategy ($27.8\% \pm 3.2\%$, with a target of 30%). The lower-hematocrit group had higher intraoperative fluid balance, higher serum lactate levels 60 minutes after cessation of CPB, lower nadirs of cardiac index in the first 24 hours, and, at age 1 year, worse Psychomotor Development Index (PDI) scores, although Mental Development Index (MDI) scores were similar between groups. Because we could not determine a specific

Abbreviations and Acronyms

CI	= confidence interval
CPB	= cardiopulmonary bypass
D-TGA	= dextro-transposition of the great arteries
MDI	= Mental Development Index
PDI	= Psychomotor Development Index
TOF	= tetralogy of Fallot
VSD	= ventricular septal defect

target hematocrit level that was optimal, we embarked on a second randomized trial of target hematocrit 25% versus 35% in a similar study population.

A companion article⁷ presents results from an intent-to-treat analysis of 124 patients, of whom 56 were assigned to a medium-hematocrit strategy at onset of low-flow CPB ($24.8\% \pm 3.1\%$, with a target of 25%) and 68 to a higher-hematocrit strategy ($32.6\% \pm 3.5\%$, with a target of 35%). These two treatment groups had similar serum lactate levels 60 minutes after cessation of CPB, nadirs of cardiac index in the first 24 hours, PDI scores, and MDI scores, although the 25% hematocrit group had higher intraoperative fluid balance and, only in a subgroup with dextro-transposition of the great arteries (D-TGA), longer hospital stay. We concluded that hemodilution to hematocrit levels of 35% compared with 25% had marginal clinical benefits and no increased risks.

In this article, we combine the data from these two trials to attempt to identify, in more quantitative terms, the relationship of hemodilution level to key postoperative and 1-year developmental outcomes.

Patients and Methods

The protocols for both hematocrit trials have been described previously^{6,7} and were similar except for the targeted hemodilution levels. We enrolled patients between November 1996 and July 2004 at Children's Hospital Boston. Eligibility criteria are summarized elsewhere and were identical in both trials.^{6,7} In brief, we included infants under age 9 months with congenital heart lesions comprised of two ventricles without aortic arch obstruction, absence of suspected or definite genetic disorders or congenital anomalies of more than minor severity, and no previous or planned cardiac surgery before the 1-year developmental evaluation. Parental informed consent was obtained according to institutional guidelines.

Of 424 eligible infants for whom informed consent was requested, 278 patients were enrolled; of these, 7 (3%) were excluded post hoc because the operation was not performed as planned or because the patient was discovered to have been ineligible after further clinical information was obtained. The remaining 271 patients underwent reparative surgical intervention according to the study protocols^{6,7} and constitute the study population. Full-flow CPB ($\sim 2.5 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$) was used during cooling and rewarming. Some patients had periods of deep hypothermic

circulatory arrest, and most had at least one period of reduced-flow CPB, for example, at approximately $0.75 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ when at deep hypothermia (rectal temperature $< 18^\circ\text{C}$). For patients in whom low-flow CPB was not used, we analyzed the hematocrit level 10 minutes after onset of cooling.

Participating infants were randomly assigned to undergo hemodilution to a hematocrit level of approximately 20% versus 30% in the first trial and approximately 25% versus 35% in the second trial. Treatment assignments were based on randomized blocks with stratification according to surgeon and diagnostic group. The method of support was assigned immediately before the operation. Perfusionists and study nurses were aware of treatment assignment. Surgeons, anesthesiologists, cardiac intensivists, and developmental psychologists were blinded to treatment assignment.

Statistical Analyses

Outcomes included the perioperative and 1-year development variables that were the primary outcome variables for at least one of the two hematocrit trials. These include serum lactate levels 60 minutes after cessation of CPB, nadir of cardiac index in the first 24 hours, and the PDI and MDI of the Bayley Scales of Infant Development at age 1 year.⁸ We also explored the relationship of hematocrit to fluid balance, use of blood products, and duration of intubation, intensive care unit stay, and hospital stay.

Analyses assessing the effects of hematocrit at the onset of low-flow CPB as a continuous variable on outcomes used linear regression, proportional hazards regression for length-of-stay variables, and generalized additive models.^{9,10} Generalized additive models are methods of non-parametric regression smoothing that allow for the assessment of any effect of hemodilution level on outcome, including nonlinear effects, as well as assessment of departure of linearity or piecewise linearity of effect. Piecewise linear (or cut point) regression models were used to model outcomes that had significant nonlinear trends with hematocrit level. Confidence intervals for cut points were based on inversion of likelihood ratio tests.¹¹ All likelihood maximizations and likelihood ratio tests searched over a grid of hematocrit levels in 0.5% increments. Quadratic regression models were also considered but did not fit the data better than either generalized additive models or piecewise linear models. We¹² have used similar methods to assess the effects of duration of deep hypothermic circulatory arrest in infant heart surgery on late neurodevelopment.

All regression analyses adjust for diagnostic group and, if statistically significant, year of operation (coded as 1996–1998, 1999–2000, 2001–2002, and 2003–2004). We also explored whether intraoperative support variables (durations of crossclamp, total support, total CPB, and circulatory arrest) and, in the case of the Bayley Scales, family social class¹³ independently predicted outcomes or served as confounders of the effect of hematocrit level on outcomes. Other tests for association used analysis of variance or Spearman rank correlation coefficients. All *P* values are

TABLE 1. Preoperative and operative characteristics of 271 patients undergoing hypothermic CPB in infant heart surgery

Variable	Mean $\pm$ SD
Preoperative characteristics	
Birth weight (kg)	3.4 $\pm$ 0.6
Gestational age (wk)	39.1 $\pm$ 1.5
Apgar score at 5 min	8.6 $\pm$ 0.9
Age at operation (d), median (range)	41 (1–269)
Sex (% male)	65
Race (% nonwhite)	20
Diagnosis, n (%)	
D-TGA group	
D-TGA, IVS	61 (23)
D-TGA, VSD	47 (17)
TOF group	
TOF	71 (26)
TOF, PA	7 (3)
Truncus arteriosus	13 (5)
VSD group	
VSD	65 (24)
Complete common AV canal	7 (3)
Ever intubated (%)	38
Overall neurologic examination result (% abnormal)	62
Operative characteristics	
Hematocrit level at onset of low-flow CPB (%)	26.5 $\pm$ 5.3
16%–20%, n (%)	37 (14)
21%–25%	84 (31)
26%–30%	85 (31)
31%–35%	49 (18)
36%–39%	16 (6)
Crossclamp time (min)	65 $\pm$ 26
Total support time (min)	108 $\pm$ 37
Total CPB time (min)	100 $\pm$ 32
Duration of circulatory arrest (min)	8 $\pm$ 13
None, n (%)	153 (56)
1–10	53 (20)
11–30	43 (16)
31–44	16 (6)
$\geq$ 45	6 (2)

CPB, Cardiopulmonary bypass; SD, standard deviation; D-TGA, dextro-transposition of the great arteries; IVS, interventricular septum; VSD, ventricular septal defect; TOF, tetralogy of Fallot; PA, pulmonary atresia; AV, atrioventricular.

2-tailed and we selected a level of significance of .05 for hypothesis testing.

Results

Descriptive statistics on preoperative and operative characteristics of the 271 combined study patients are included in Table 1. Hematocrit levels at the onset of low-flow CPB ranged from 16% to 39% and were not associated with diagnostic group ($26.6\% \pm 5.2\%$, mean $\pm$ SD, for the

TABLE 2. Perioperative and 1-year outcomes of 271 patients undergoing hypothermic CPB in infant heart surgery

Variable	n	Mean $\pm$ SD
Perioperative outcomes		
Intraoperative fluid balance (mL)	244	401 $\pm$ 259
Intraoperative blood products (mL), median (range)	270	208 (25–1383)
Serum lactate at 60 min after CPB (mmol/L)	239	2.9 $\pm$ 1.6
Nadir of cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	102	3.1 $\pm$ 1.1
Postoperative blood products (mL), median (range)	271	111 (0–3551)
One-year outcomes		
PDI	215	86.2 $\pm$ 15.7
MDI	216	93.9 $\pm$ 12.4

CPB, Cardiopulmonary bypass; SD, standard deviation; PDI, Psychomotor Development Index; MDI, Mental Development Index.

D-TGA group; $26.2\% \pm 5.5\%$ for the tetralogy of Fallot [TOF] group; and $26.9\% \pm 5.2\%$ for the ventricular septal defect [VSD] group; analysis of variance $P = .64$) or with duration of crossclamp (Spearman rank correlation $r = 0.04$, $P = .53$), total support ($r = 0.03$, $P = .61$), total CPB ($r = 0.03$, $P = .68$), or circulatory arrest ($r = 0.004$, $P = .95$). One infant (0.4%) died within 1 month of the operation.

Perioperative Outcomes

Descriptive statistics on perioperative and 1-year outcomes are included in Table 2. We assessed the relationship of hematocrit level at the onset of low-flow CPB to intraoperative fluid balance. In generalized additive models adjusting for diagnostic group and year of operation, we found no significant departures from linearity ($P = .83$). In linear regression models adjusting for diagnostic group and year of operation, increasing hematocrit level was significantly associated with decreasing fluid balance; each 1-point increase in hematocrit level was associated with an 11.8-mL decrease in intraoperative fluid balance (95% confidence interval [CI] = 5.5–18.1 mL; $P < .001$, Figure 1, A). Independent predictors of higher intraoperative fluid balance included diagnostic group (D-TGA highest, TOF intermediate, VSD lowest; $P < .001$), later year of operation ($P < .001$), and longer crossclamp, total support, and total CPB times ($P < .001$ for each), but not duration of circulatory arrest. Inclusion of these support times in the multivariable linear model further increased the strength of the relationship of higher hematocrit at onset of low-flow CPB to lower intraoperative fluid balance.

Although higher fluid balance was significantly associated with longer time until endotracheal intubation, intensive care unit discharge, and hospital discharge, hematocrit

Figure 1. Scatterplots of outcomes as a function of hematocrit level at the onset of low-flow CPB. The panels represent intraoperative fluid balance (A), serum lactate levels at 60 minutes after cessation of CPB (B), Psychomotor Development Index (C), and Mental Development Index (D). The *solid lines* were derived through generalized additive models, with pointwise 95% confidence limits for hematocrit effects denoted as *dashed lines*. The *dot-dash lines* denote the fitted linear regression models. In the case of Psychomotor Development Index, the *dot-dash line* denotes the fitted piecewise linear regression model, based on the optimal cut point of 23.5% hematocrit. The *P* values assess the strength of the relationship between hematocrit on outcome in adjusted linear regression models. For Psychomotor Development Index, the top *P* value corresponds to the effect before and the bottom *P* value corresponds to the effect after the optimal cut point of 23.5% hematocrit. All models adjust for diagnostic group and models for intraoperative

fluid balance also adjust for year of operation. Generalized additive model fits and linear regression model fits are plotted for average values of these adjustment factors.

level at the onset of low-flow CPB was not an independent predictor of these measures of prolonged recovery in multivariable models adjusting for diagnosis or year of operation. Furthermore, analyses within diagnostic groups also did not show associations between hematocrit level and length-of-stay variables.

We assessed the relationship of hematocrit level at the onset of low-flow CPB to serum lactate levels at 60 minutes after cessation of CPB. In generalized additive models adjusting for diagnostic group, we found no significant departures from linearity ($P = .73$). In linear regression models adjusting for diagnostic group, higher hematocrit level was marginally associated with lower lactate level; each 1-point increase in hematocrit level was associated with a 0.027 mmol/L decrease in serum lactate levels at 60 minutes after cessation of CPB (95% CI = -0.003 - 0.057 mmol/L; $P = .08$, Figure 1, B). Independent predictors of higher serum lactate included diagnostic group (D-TGA highest, TOF intermediate, VSD lowest; $P < .001$), longer total support time ($P = .009$), and longer duration of circulatory arrest ($P < .001$). Inclusion of these support times in the multivariable linear model increased the strength of the relationship of higher hematocrit level at onset of low-flow CPB to lower serum lactate levels.

Nadir of cardiac index was measured in only 102 patients. Adjusting for diagnostic group, we found no significant departures from linearity of the effects of hematocrit level on nadir of cardiac index ($P = .44$) and no significant linear effects of hematocrit level on nadir of cardiac index ($P = .24$). The only independent predictor of nadir of cardiac index was diagnostic group (D-TGA lowest, TOF intermediate, and VSD highest; $P < .001$).

We measured the use of blood products intraoperatively and in the postoperative period. Adjusting for diagnostic group and, for intraoperative blood products only, year of operation, there were no significant departures from linearity and no significant linear effects in the relationships of hematocrit level to intraoperative or postoperative blood product use. Independent predictors of higher intraoperative blood products included diagnostic group (D-TGA highest, TOF intermediate, VSD lowest; $P < .001$), later calendar year of operation ($P = .004$), and longer crossclamp, total support, and total CPB times ($P < .001$ for each), but not duration of circulatory arrest. Independent predictors of higher postoperative blood products included longer crossclamp, total support, total CPB, and circulatory arrest times ($P < .001$ for each). Inclusion of these support times in the multivariable linear models did not affect the lack of sig-

nificant association between hematocrit levels and postoperative blood products.

One-year Outcomes

We assessed the relationship of hematocrit at the onset of low-flow CPB to PDI scores at age 1 year. In generalized additive models adjusting for diagnostic group, we found significant departures from linearity ($P = .008$). Evaluation of piecewise linear models over a grid of hematocrit cut points led to an optimal cut point of 23.5%, with a 95% CI from 21.0% to 29.5%. In a piecewise linear model, each 1-point increase in hematocrit up to 23.5% was associated with a 2.6-point increase (slope) in PDI scores (95% CI = 1.1-4.2; $P < .001$). However, increasing hematocrit level above 23.5% was not significantly associated with PDI scores (slope = -0.2 , 95% CI -0.8 - 0.3 ; $P = .42$), and PDI scores had effectively reached a plateau by a hematocrit level of 23.5% (Figure 1, C). The two slopes (ie, below and above hematocrit levels of 23.5%) were significantly different ($P = .003$). Generalized additive models showed no significant evidence of departure from the piecewise linear model ($P = .32$). Choice of other cut points led to similar inferences. Intraoperative support times and social class did not serve as significant independent predictors of PDI scores.

We assessed the relationship of hematocrit at the onset of low-flow CPB to MDI scores at age 1 year. Adjusting for diagnostic group, we found no significant departures from linearity of the effects of hematocrit on MDI scores ($P = .34$) and no significant linear effects of hematocrit on MDI ($P = .26$) (Figure 1, D). Higher family social class was independently associated with higher MDI scores ($P < .001$).

Discussion

We found that PDI scores at age 1 year varied nonlinearly with hematocrit levels, with significantly increasing scores up to 23.5% hematocrit and a plateau effect beyond 23.5% hematocrit, based on a piecewise linear model. Lower hematocrit levels were significantly associated with higher fluid balance and marginally associated with higher serum lactate levels at 60 minutes after CPB, but not associated with nadir of cardiac index in the first 24 hours, blood products given, or MDI scores. It may be appropriate to target hematocrit level at the onset of low-flow CPB to be at least 24%, inasmuch as lower hematocrit levels are associated with worse PDI scores and a tendency for higher lactate levels, whereas higher hematocrit levels were not associated with adverse events or outcomes.

The correlation/linear regression methods used in previous studies, which force a linear fit to the relationship between hemodilution and outcomes, are problematic if there is a nonlinear trend between these variables. In particular, the overall slope or correlation is a weighted average of the slopes or correlations over the whole range of

hematocrit values, which could underestimate the effects of hemodilution over certain ranges of hematocrit values if there are nonlinear trends. Our use of nonparametric regression smoothing and piecewise linear regression provided an opportunity to identify potential cut points in these associations.

We found no relationship of hematocrit level at the onset of low-flow CPB with usage of blood products in the operating room or during the postoperative period. Animal models of hematocrit strategy have shown that hemodilution not only reduces oxygen-carrying capacity, but also reduces osmolality, viscosity, and perfusion pressure, as well as diluting platelets and coagulation factors.^{4,14} The lack of association of hematocrit levels with blood product use may reflect improved hemostasis with higher hematocrit levels.

Laboratory studies have demonstrated the important interaction of hematocrit with temperature, pH strategy, and duration of circulatory arrest or very reduced flow.^{15,16} Specifically, animal models have demonstrated that it is possible to compensate for the reduced oxygen-carrying capacity of low hematocrit by increasing oxygen availability by the pH-stat strategy or by increasing flow rate, reducing duration of circulatory arrest, or reducing temperature. In both hematocrit trials, we used the pH-stat strategy, deep hypothermia in many patients, and minimal periods of extended circulatory arrest or very low-flow CPB. These aspects of the intraoperative milieu, together with the potential inclusion of some infants with undetected genetic syndromes, may have limited our power to detect effects of hematocrit on some outcomes.

Our analyses should be interpreted in light of several additional limitations. Both hematocrit trials were conducted in a single center and included only infants undergoing reparative cardiac surgery for congenital heart defects involving two ventricles without aortic arch obstruction. These aspects of the study could limit generalizability to other centers and congenital heart lesions. Furthermore, although we excluded infants with known or suspected genetic or congenital anomalies, the study protocols did not require fluorescent in situ hybridization studies to exclude genetic disorders; the inadvertent inclusion of some children with genetic disorders could have diminished the effect of hematocrit level on 1-year neurodevelopmental outcomes.

In summary, we found that the effect of hemodilution level on PDI scores is nonlinear, with improving scores with increases in hematocrit level at the onset of low-flow CPB up to approximately 24%, followed by a plateau. Increasing hematocrit levels were also marginally related to a reduction in serum lactate levels 60 minutes after cessation of CPB. This study cannot ascertain a universally optimal hematocrit level because of potential influences of patient characteristics and other intraoperative factors, but at Children's Hos-

pital Boston, we try to ensure that hematocrit level will be above 25% at commencement of CPB and during CPB and rewarming. Future multicenter investigations should ascertain late neurodevelopmental status after infant cardiac surgery and study other populations, including adults, to help to clarify optimal hematocrit levels during CPB.

We thank our perfusionists: Willis G. Gieser, CCP, Robert A. LaPierre, BS, CCP, Robert J. Howe, BS, CCP, Gregory S. Matte, CCP, and William L. Regan; our nursing staff in the Cardiac Intensive Care Unit for assistance with adherence to the protocols; Ludmila Kyn for database and statistical programming; Donna Donati, Donna Duva, and Lisa-Jean Buckley for data management; Kathleen Alexander for project coordination; and families and children in the cohort for their time and effort.

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