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Effects of Extreme Hemodilution during Cardiac Surgery on Cognitive Function in the Elderly

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Background: **Strategies for neuroprotection including hypothermia and hemodilution have been routinely practiced since the inception of cardiopulmonary bypass. Yet postoperative neurocognitive deficits that diminish the quality of life of cardiac surgery patients are frequent. Because there is uncertainty regarding the impact of hemodilution on perioperative organ function, the authors hypothesized that extreme hemodilution during cardiac surgery would increase the frequency and severity of postoperative neurocognitive deficits.**

Methods: **Patients undergoing coronary artery bypass grafting surgery were randomly assigned to either moderate hemodilution (hematocrit on cardiopulmonary bypass ≥27%) or profound hemodilution (hematocrit on cardiopulmonary bypass of 15–18%). Cognitive function was measured preoperatively and 6 weeks postoperatively. The effect of hemodilution on postoperative cognition was tested using multivariable modeling accounting for age, years of education, and baseline levels of cognition.**

Results: **After randomization of 108 patients, the trial was terminated by the Data Safety and Monitoring Board due to the significant occurrence of adverse events, which primarily involved pulmonary complications in the moderate hemodilution group. Multivariable analysis revealed an interaction between hemodilution and age wherein older patients in the profound hemodilution group experienced greater neurocognitive decline ($P = 0.03$).**

Conclusions: **In this prospective, randomized study of hemodilution during cardiac surgery with cardiopulmonary bypass in adults, the authors report an early termination of the study because of an increase in adverse events. They also observed greater neurocognitive impairment among older patients receiving extreme hemodilution.**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

THE advent of hypothermic cardiopulmonary bypass (CPB) has made intentional hemodilution a standard practice, because it is believed that the increase in blood viscosity without hemodilution adversely affects microcirculatory flow. In the 1980s and 1990s, the acceptable level of CPB hemodilution was decreased to hematocrit values less than 18% as a consequence of the heightened concern of viral transmission through blood transfusion. During the same period, a healthy canine CPB model study suggested that the hematocrit at which cerebral metabolism became delivery dependent was approximately 14% during normothermic CPB and 11% during CPB at 28°C.[1,2] However, physiologically important changes in cerebral oxygen supply were reported in subsets of the animals at hematocrits as high as 18%.[1] Limits to hemodilution were also suggested by other animal data,[3,4] but, in general, the neurologic consequences of extreme hemodilution, a common clinical practice during CPB, were largely unknown.

Although mortality for patients undergoing cardiac surgery continues to decline, unacceptable rates of postoperative neurocognitive decline remain, occurring in 53% of patients immediately after surgery and in 30% after 6 months.[5] Quality of life is also diminished for these patients, who anticipate that postoperative improvements in physical status will generally improve their lives.[6] Potential mechanisms for this neurocognitive injury after cardiac surgery with CPB include cerebral hypoperfusion, air and particulate embolism, ischemia–reperfusion injury, and an exaggerated inflammatory response. Given the inconclusive data on the effect of hemodilution on neurologic outcomes (at the inception of the study), particularly in the elderly and in the setting of ischemia–reperfusion during CPB, we hypothesized that extreme hemodilution during CPB for cardiac surgery adversely affects neurocognitive outcome after cardiac surgery.

Materials and Methods

Study Population

Subsequent to approval by the Duke University Health System Institutional Review Board (Durham, NC) and informed consent, patients older than 65 yr undergoing coronary artery bypass graft surgery with CPB were enrolled into this clinical trial, designed as a prospective,

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randomized, blinded, interventional trial. Patients were randomized to two treatment groups: (1) moderate hemodilution (MH), wherein the hematocrit on CPB was maintained at 27% or greater; and (2) profound hemodilution (PH), wherein the hematocrit on CPB was maintained at 15–18%. A group assignment schedule was prepared using a randomization function in SAS® version 9.1 (SAS, Cary, NC) and stored in consecutively numbered sealed envelopes until allocation. Assignments were stratified by two sex groups and five age groups (65–69, 70–74, 75–79, 80–84, and 85+ yr). Within strata, the randomized assignments were balanced in varying block sizes of 6, 8, and 10. Although operating room personnel were aware of the patient's treatment assignment, both the patient and the investigators responsible for evaluating the neurologic/neurocognitive status of the patient were blinded to the treatment assignment. Patients were excluded from participation if they had a history of symptomatic cerebrovascular disease (*e.g.*, stroke with a residual deficit), psychiatric illness (any clinical diagnoses requiring therapy), renal failure (serum creatinine >2 mg/dl), active liver disease (liver function tests >1.5 times the upper limit of normal), alcoholism (>2 drinks/day), or chronic anemia (hematocrit <30%); were unable to read; or had less than a seventh grade education.

Patient Management

Anesthesia was induced and maintained with midazolam, fentanyl, and isoflurane. All patients underwent nonpulsatile hypothermic (30°–32°C) CPB. The perfusion apparatus consisted of a Cobe CML membrane oxygenator (COBE Chem Labs, Lakewood, CO), Sarns 7000 MDX pump (3M Inc., Ann Arbor, MI), and Pall SP3840 arterial line filter (Pall Biomedical Products Co., Glen Cove, NY). Perfusion was maintained at pump flow rates of 2–2.4 $l \cdot min^{-1} \cdot m^2$ throughout CPB to maintain a mean arterial pressure at 50–80 mm Hg. The pump was primed with crystalloid and arterial blood gases were measured every 15–30 min to maintain arterial carbon dioxide partial pressures of 35–40 mm Hg, unadjusted for temperature (α-stat), and oxygen partial pressures of 150–250 mm Hg.

Hemodilution Management

Before the initiation of CPB, the estimated blood volume for each patient was calculated as described in table 1. For patients randomized to MH, the volume of packed erythrocytes to be added to achieve a hematocrit of 27% or greater was calculated as

$$\text{Volume} = [((\text{estimated blood volume} + \text{pump prime}) \times \text{desired hematocrit}) - (\text{estimated blood volume} \times \text{pre-CPB hematocrit})]/\text{hematocrit of transfused blood}.$$

For patients randomized to PH, the volume of blood to be removed to achieve a hematocrit of 15–18% was calculated as

$$\text{Volume} = [(\text{estimated blood volume} \times (\text{pre-CPB hematocrit} - 0.17)) - (0.17 \times (\text{CPB prime} + \text{volume added}))]/\text{pre-CPB hematocrit},$$

where volume added to the pump prime was 500–1,000 ml hetastarch solution, 6%.

In the MH group, packed erythrocytes were added to the pump prime (if needed) before the onset of CPB. In the PH group, the calculated volume of heparinized blood was drained *via* the venous circuit into storage bags upon initiation of CPB. Harvested blood was stored at room temperature and added back to the venous reservoir immediately before separation from CPB. Blood was also returned to the circuit during CPB to maintain a hematocrit of 15% or greater or if the patient's clinical condition dictated the transfusion of blood (*e.g.*, profound hypotension unresponsive to phenylephrine or mixed venous saturation <50% for more than 10 min).

Table 1. Calculations to Derive Estimated Blood Volume

Desirable weight (DW)
For men: $7.582 \times e^{(0.01325 \times \text{body height in cm})}$
For women: $7.090 \times e^{(0.01309 \times \text{body height in cm})}$
Deviation from desirable weight (DDW)
$DDW = 100 \times ((\text{actual body weight} - DW)/DW)$
Body volume–to–body weight ratio (BVBWR)
$BVBWR = 45.2 + (25.3 \times e^{(-0.0198 \times DDW)})$
Estimated blood volume (EBV)
$EBV = BVBWR \times \text{actual body weight}$

Measurement of Neurocognitive Function

Trained psychometricians blinded to the treatment group individually examined patients with a battery of five cognitive tests on the day before surgery and again at 6 weeks after CPB. Instruments included the Short Story module of the Randt Memory Test, Digit Span subtest of the Wechsler Adult Intelligence Scale–Revised Test, Modified Visual Reproduction Test from the Wechsler Memory Scale, Digit Symbol subtest of the Wechsler Adult Intelligence Scale–Revised Test, and Trail Making Test (Part B).

Statistical Analysis

To characterize cognitive function over time while minimizing potential redundancy in the cognitive measures, a factor analysis was performed on the 10 cognitive test scores from baseline. The 10 scores were incorporated into a principal components analysis using SAS Proc Factor, with orthogonal rotation (a linear transformation of the data) to produce uncorrelated factors. The factor analysis was conducted on the enrolled patients in this study, and scoring coefficients for all time points were determined using this sample's baseline rotated factor scores; thus, cognitive domains remained consis-

tent over time. We chose a four-factor solution, which accounts for 84% of the variability in the original 10 test scores and represents four cognitive domains: (1) verbal memory and language comprehension, short-term and delayed; (2) attention, psychomotor processing speed, and concentration; (3) abstraction and visuospatial orientation; and (4) figural memory. Two summary measures were calculated to represent cognitive function: (1) "Cognitive deficit" (the binary outcome) was defined as a decline of 1 SD or more in performance on at least one of the four domains. (2) To quantify overall cognitive function and the degree of learning (*i.e.*, practice effect from repeated exposure to the testing procedures), a "baseline cognitive index" was first calculated as the sum of the four preoperative domain scores. A continuous change score (the continuous outcome) was then calculated by subtracting the baseline from the follow-up cognitive index.

Categorical and continuous demographic characteristics were compared between treatment groups with Pearson chi-square and *t* tests, respectively. Continuous variables are reported as mean ± SD or as median with interquartile range (IQR). The effect of the hemodilution group on postoperative cognition was tested using variable linear and logistic regression modeling accounting for age, years of education, and baseline cognition; interactions with age were also examined. Secondary *post hoc* analyses were similarly conducted using the area under the curve for hematocrit below the pre-CPB value as a predictor variable. This variable was chosen because of an abundance of more recent (after the majority of study enrollment) literature indicating that nadir hematocrit was a predictor of adverse outcome after cardiac surgery.[7–11] $P < 0.05$ was considered significant; all analyses were performed with SAS® version 9.1. No adjustment was made for multiple comparisons because all *post hoc* analyses were considered exploratory. Because primary outcome comparisons were conducted only after study termination and not during the yearly Data Safety and Monitoring Board review, statistical penalties were not applied for interim analysis.

We expected that the incidence of cognitive deficit in patients older than 65 yr would be approximately 35%. We hypothesized that the profound hemodilution strategy would increase this incidence to 50%, and a sample size of 170 per group would yield power of 80% at a significance level of 0.05 to detect this difference. To allow for a 10% loss to follow-up, we intended to recruit a total of 374 patients.

Results

From June 14, 1999 to February 12, 2002, a total of 121 patients were consented to participate in the study (fig. 1 table 2). Thirteen of these patients were not subsequently enrolled (refused neurologic testing = 6, changed mind = 4, exclusion criteria developed = 1, surgical decision = 1, change in surgical schedule = 1). At the third scheduled review of the Data Safety and

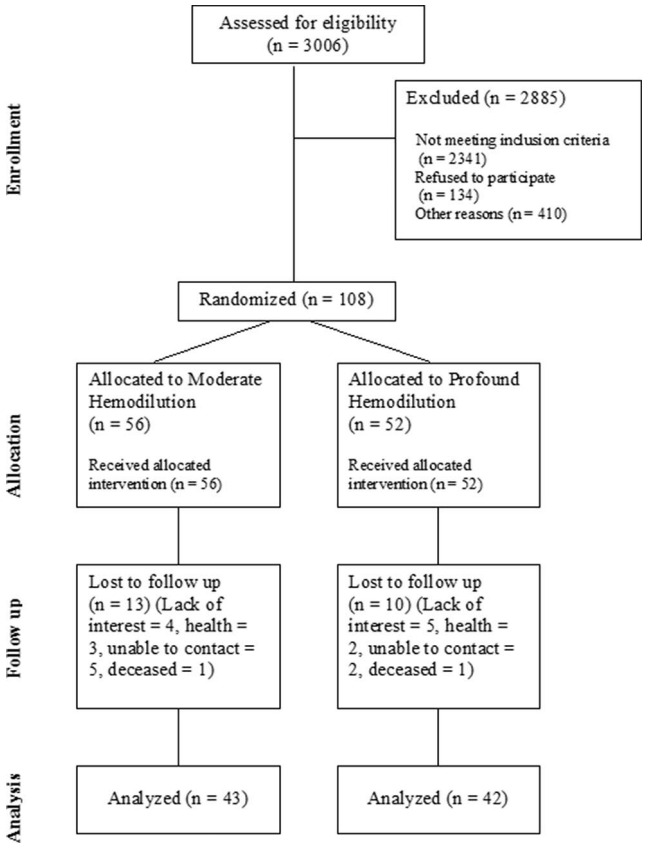

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) diagram showing the flow of participants.

Table 2. Demographic Characteristics of the Enrolled Subjects

Variable	Moderate Hemodilution	Profound Hemodilution
Age (SD), yr	69.4 (6.9)	69.0 (6.1)
Sex, % female	19.6	21.6
Race, % white	91	90
Weight (SD), kg	81.1 (18.0)	85.8 (21.1)
History of hypertension, %	66	71
Diabetes, %	36	24
Previous MI, %	45	50
Congestive heart failure, %	20.4	10.9
Ejection fraction (SD)	55 (10)	58 (10)
Charlson comorbidity index (SD)	0.63 (0.93)	0.62 (0.84)
Number of grafts, %		
1	7	0
2	9	14
3	54	51
4	27	13
5	4	5
Cross clamp time (SD), min	72 (22)	71 (25)
CPB time (SD), min	121 (29)	120 (40)
Years of education (SD)	13.3 (3.5)	13.4 (3.9)
Preoperative cognitive index (SD)	−0.04 (0.51)	0.06 (0.51)
Preoperative hematocrit (SD), %	38.9 (9.5)	39.4 (7.8)

CPB = cardiopulmonary bypass; MI = myocardial infarction.

Table 3. Multivariable Logistic Regression Model Predicting Cognitive Deficit at 6-Week Follow-up

Variable	*df*	Parameter Estimate (95% Confidence Limits)	*P* Value
Profound hemodilution	1	6.99 (1.24 to 12.76)	0.02
Preoperative cognitive index	1	0.64 (−0.58 to 1.86)	0.30
Age	1	0.05 (−0.04 to 0.13)	0.30
Years of Education	1	−0.09 (−0.25 to 0.07)	0.27
Age × profound hemodilution	1	−0.10 (−0.19 to −0.02)	0.02

Monitoring Board, termination of the trial was recommended because of an increase in the incidence of adverse events. At the point of termination, 56 patients were randomized to the MH group and 52 were randomized to the PH group (n = 108).

Demographic characteristics of the randomized patients are listed in table 2; as expected from randomization, no significant differences were seen. The mean hematocrits during CPB for the PH and MH groups were 18.0 ± 1.7% and 26.9 ± 2.8%, respectively. Mean arterial pressure during CPB in the MH group was 55.6 ± 6.9 mm Hg compared with 52.4 ± 5.2 mm Hg in the PH group ($P = 0.11$). The mean volume of blood removed in the PH group before the onset of CPB was 1578 ml (IQR, 640–2,000 ml). Eighty-nine percent of the MH patients were transfused with homologous blood products compared with 88% of the PH patients ($P = 0.86$). Intraoperatively and postoperatively, the MH group received a median of 900 ml (IQR, 600–1,500 ml) packed erythrocytes compared with 900 ml (IQR, 600–1,900 ml) ($P = 0.78$); similarly, there were no differences in the transfusion of fresh frozen plasma or platelets.

Cognitive deficits, defined as a decline of 1 SD or more in performance on at least one of the four domains, were present at 6 weeks after surgery in 37.5% of patients randomized to MH and in 42.5% of patients randomized to PH ($P = 0.65$). The continuous cognitive score was also not significantly different between the treatment groups. Multivariable analysis accounting for the covariable effects of age, baseline level of cognition, and years of education, however, revealed a significant treatment group–by–age interaction, such that older patients in the PH group were more likely to experience cognitive decline (binary outcome: $P = 0.03$, table 3; continuous outcome: $P = 0.02$).

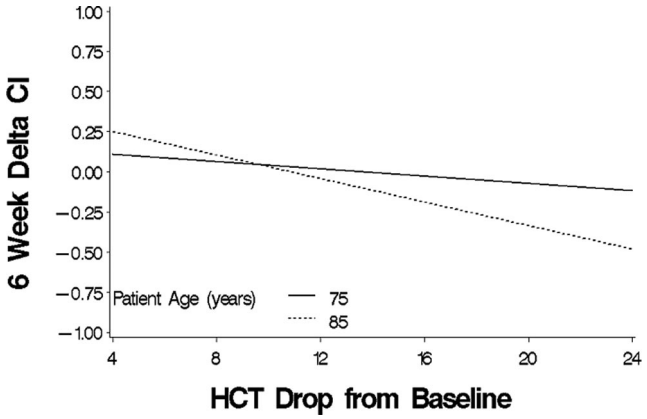

Fig. 2. Older patients with a greater hematocrit decrease from baseline were more likely to experience cognitive decline. HCT = hematocrit; Delta CI = (6-week − preoperative cognitive index).

Post hoc analyses conducted using the area under the curve for hematocrit below the pre-CPB value as a predictor variable and adjusting for the effects of age, baseline level of cognition, and years of education also revealed a significant interaction between hematocrit-area below baseline and age ($P = 0.02$). To determine whether the maximum decrease in hematocrit from baseline was as important as the area under the curve (decrease + duration), additional modeling was conducted using only the maximum decrease in hematocrit from baseline as the predictor variable. The mean decrease in the hematocrit from baseline in the MH group was 11.7 ± 4.5% *versus* 19.9 ± 4.6% in the PH group ($P < 0.001$). Again, a significant interaction with age was detected; a greater decrease in the cognitive change score was present in older patients with a greater decrease from baseline hematocrit (table 4 and fig. 2). To investigate the possibility of a nonlinear association between hematocrit decrease and cognitive change, an analysis using restricted cubic splines was performed in the subset of patients who were aged 70 yr or older (n = 51). Restricted cubic splines, which are smooth at the joint points, or knots (slope is allowed to vary at these points) and which are constrained to be linear in the

Table 4. Multivariable Linear Regression Model Demonstrating That the Maximum Decrease in Hematocrit from Baseline Is a Significant Predictor of the Change in Cognitive Index at 6 Weeks

Variable	*df*	Parameter Estimate (95% Confidence Limits)	SE	*P* Value
Intercept		−1.678	0.983	—
Preoperative cognitive index	1	−0.261 (−0.428 to −0.094)	0.084	0.003
Age	1	0.028 (−0.004 to 0.057)	0.014	0.053
Years of education	1	0.023 (0.001 to 0.045)	0.011	0.043
Pre-CPB Hct	1	−0.018 (−0.036 to 0.0003)	0.009	0.054
Maximum decrease in Hct	1	0.211 (0.084 to 0.338)	0.064	0.002
Age × maximum decrease in Hct	1	−0.003 (−0.005 to −0.001)	0.001	0.002

CPB = cardiopulmonary bypass; Hct = hematocrit.

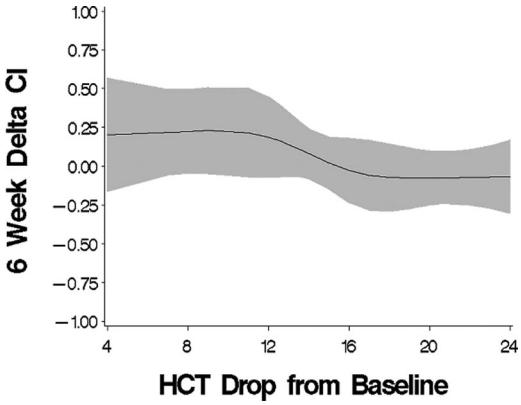

Fig. 3. Decline in cognition with increasing change in hematocrit from baseline. The *shaded area* represents 95% confidence intervals. The threshold for cognitive decline seems to be at an approximately 12% decrease from baseline hematocrit. HCT = hematocrit; Delta CI = (6-week − preoperative cognitive index).

tails, can greatly improve the fit of the model.[12] Based on the size of the data set, four knots were placed at the 10th, 25th, 75th, and 90th percentiles. Figure 3 shows the resulting fitted line with 95% confidence intervals indicating that cognitive decline was relatively unchanged until the decline in hematocrit from baseline exceeded approximately 12% points.

At the third Data Safety and Monitoring Board review, it was noted that the MH group was experiencing a greater number of pulmonary complications as well as a trend to a greater number of serious adverse events (table 5). At the request of the Data Safety and Monitoring Board, we also compared the occurrence of adverse events in the study groups with events in a group of patients (n = 323) enrolled in a contemporaneous noninterventional trial. The greater occurrence of pulmonary complications was even more significant (P = 0.002) when the MH group was compared with this nonintervened group. This difference persisted (P = 0.05) when the MH group was compared with a subset of the nonintervened patients who were matched to the hemodilution patients on study date, age, and CPB time (cross clamp time, Hannan score, Parsonnet score, and Charlson comorbidity index were also similar; mean hematocrit during CPB = 23.5 ± 3.7%). The pulmonary complications that varied the most between the MH and nonintervened groups were the occurrence of postoperative pneumonia (13.3% *vs.* 5.9%) and pulmonary edema (26.7% *vs.* 8.8%). MH patients with postoperative pneumonia received a median of 4,500 ml (IQR, 3,600–5,400 ml) packed erythrocytes, and those with pulmonary edema received 3,300 ml (IQR, 1,050–10,299 ml) packed erythrocytes. The overall transfusion rate in the MH (89%) and PH (88%) groups was also significantly higher than the matched control group (69%; P = 0.02).

Discussion

To our knowledge, this is the first prospective, randomized study of hemodilution during cardiac surgery with CPB in adults. This trial was terminated early because of an increase in adverse events in the moderate hemodilution group. Despite the incomplete enrollment, we found that older patients experiencing profound hemodilution were more likely to experience cognitive decline. In secondary analyses, an association between the maximum decrease in hematocrit from baseline and neurocognitive decline in the elderly was also detected; a decrease in hematocrit of 12% points or greater from baseline approximated the threshold for this cognitive decline.

The effects of hemodilution during CPB on ischemic neurologic injury have been studied in both animals and humans. Although early animal studies indicated a potential benefit to hemodilution, strengthening the belief that hemodilution during cardiac surgery was without consequence,[13,14] most of these studies were limited in that they did not mimic CPB or reduce hematocrit below 30%. In a landmark study in healthy dogs, Cook *et al.*,[2] attempting to define the "critical hematocrit," reported that increases in cerebral blood flow (CBF) compensated for the decreased arterial oxygen content from hemodilution and that cerebral oxygen delivery was maintained to a hematocrit of approximately 14% during normothermic CPB. Subsequent study by these same investigators

Table 5. Adverse Events in the Hemodilution Treatment Groups

	Moderate Hemodilution		Profound Hemodilution		*P* Value	
	Percent of Events	Percent of Patients	Percent of Events	Percent of Patients	Events	Patients
Cardiac	34.5	40.0	35.5	34.6	0.90	0.56
Hematology	8.3	7.3	6.5	5.8	0.67	0.75
Immune	7.1	7.3	12.9	13.5	0.24	0.29
Neurologic	2.4	3.6	3.2	3.9	0.76	0.95
Gastrointestinal	1.2	1.8	1.6	1.9	0.83	0.97
Genitourinary	2.4	3.6	0	0	0.22	0.17
Pulmonary	17.9	16.4	4.8	5.8	0.02	0.08
Renal	1.2	1.8	3.2	3.9	0.39	0.53
Other	25.0	23.6	32.3	28.9	0.33	0.54
Serious events	51.1	31.0	37.1	34.3	0.09	0.76
Unexpected events	58.3	35.0	62.9	50.0	0.58	0.19

demonstrated that cerebral oxygen demand was maintained to a hematocrit of 11% when hypothermia was applied. However, with progressive temperature reduction, a progressively smaller increase in CBF was seen, and "physiologically important changes in cerebral oxygen supply" were reported at hematocrits of 18, 15, and 12% with temperatures of 38°, 28°, and 18°C, respectively.[1] Limits to the extent of hemodilution were also described by Lee *et al.*,[4] who reported that hemodilution to a hematocrit of 30% reduced cerebral infarct volumes in a dog model, but the benefit was reversed when the hematocrit was further reduced to 25%. Similarly, Reasoner *et al.*[3] found an increase in hemispheric infarct size after middle cerebral artery occlusion in rabbits when marked hemodilution (hematocrit = 18%) was used. More recently, Homi *et al.*[15] also hemodiluted rats surgically prepared for CPB to a hematocrit of 18% and reported both worsened functional neurologic performance and greater cerebral infarct volumes 24 h after middle cerebral artery occlusion, when compared with control animals maintained at a hematocrit of 33%.

The deleterious consequences of extreme hemodilution during CPB in humans have also been recently (subsequent to study inception and the majority of enrollment) highlighted by a series of retrospective database studies. In virtually every outcome examined, an independent, direct association between the degree of hemodilution during CPB and the adverse outcome of interest was identified. For example, Karkouti *et al.*,[11] studying 10,949 patients undergoing cardiac surgery with CPB, reported a 10% increase in the odds of experiencing a perioperative stroke with each percent decrease in hematocrit. When acute renal failure was examined, these same investigators reported a 230% increase in the odds of developing acute postoperative renal failure for those with a CPB nadir hematocrit less than 21%.[10] Interestingly, the odds of developing renal failure was also increased in those with a hematocrit greater than 25%, suggesting that an "optimal" hematocrit to manage this outcome might be somewhere between 21% and 25%. The lowest hematocrit on CPB has also been associated with greater in-hospital mortality[7,8] and reduced survival up to 6 yr after surgery.[9] A single prospective randomized trial in infants confirms the deleterious effects of extreme hemodilution. In that study, 147 infants were randomized to a hematocrit of 20% or 30% at the onset of low-flow CPB using a pH-stat strategy.[16] The lower hematocrit group had lower nadirs of cardiac index, higher serum lactate levels 60 min after CPB, and at age 1 yr, worse scores on a psychomotor development index. In contrast, a single retrospective study found no correlation between cognitive performance and hematocrit levels preoperatively, 30 min after CPB, 10 min after the end of CPB, or on the first postoperative day.[17] However, only 1 of 111 patients in that study had a hematocrit on CPB less than 20%.

Acute isovolumic anemia to a hematocrit of 15–18% (the same range as that of the PH group in our study) in healthy volunteers has been reported to increase reaction time and degrade immediate and delayed memory during cognitive testing.[18] These slowed responses are thought to result not from a nonspecific effect on attention but from impaired central processing as detected by an increase in the P300 evoked potential latency.[19] Although the reported effects on cognition were transient and reversible by the administration of oxygen or erythrocytes, subjects were severely anemic for only brief periods of time, and it was uncertain whether protracted periods of anemia (as seen with CPB) would have produced greater impairment. In the setting of cardiac surgery with CPB, it is likely that any deleterious effect of severe anemia is compounded by CPB-related alterations in cerebral physiology. Based on the work of Cook *et al.*,[20] it is widely believed that during CPB, an increased CBF as a consequence of hemodilution, maintains cerebral oxygen delivery. Furthermore, a close coupling of oxygen delivery and demand is seen in normothermic CPB, but this coupling is lost during hypothermic CPB; CBF is unchanged with the addition of hypothermia despite the large decrease in cerebral metabolic rate.[20,21] Because CBF is uniformly increased with severe anemia during CPB, the worsening of cognitive function seen in these patients could then be a consequence of an increased delivery of cerebral emboli. Pathologic and Doppler studies[22,23] have long supported the association between embolic load and neurocognitive injury after cardiac surgery, but the clinical relevance of this association has been questioned by others.[24] Although data clearly demonstrating an increase in embolic load with severe anemia during CPB are lacking, several studies suggest that such an association is plausible. In a dog study examining the relation between CPB flow rate and cerebral embolization, it was noted that tissues with high blood flow received more emboli than tissues with lower blood flow.[25] Similarly, in a study evaluating the safety of a perfluorocarbon emulsion administered during CPB, an increase in CBF seen after hemodilution and emulsion administration was accompanied by a greater number of transcranial Doppler–detected cerebral emboli.[26]

The impact of aging upon CBF and oxygenation in the setting of severe anemia or CPB has not been widely studied, so we can only speculate as to the reasons for our finding that extreme hemodilution was detrimental only in the elderly. A study in rats has shown that the cerebral hyperemic response to anemia is preserved in the aged, whereas a study of 12 subjects undergoing CPB revealed that advancing age further increased the magnitude of this hyperemia, albeit in the postoperative period.[27,28] The greater increases in CBF seen in the elderly may again be simply associated with a larger

embolic load and, therefore, greater neurocognitive injury.

The principal limitation to our study is the failure to reach the targeted enrollment as a consequence of the safety concerns. Nevertheless, the early termination of our study because of an increase in pulmonary complications, notably pneumonia and pulmonary edema, suggests that aggressive transfusion to maintain a hematocrit of 27% or greater during CPB may not be prudent. The association between packed erythrocyte transfusion and nosocomial pneumonia has been reported previously, with most studies suggesting a transfusion threshold of 3–4 units before the increased risk of infection is evident.[29–31] In the patients with postoperative pulmonary edema who also received large volumes of packed erythrocytes, transfusion-related acute lung injury is a consideration because coronary artery bypass graft surgery and massive transfusion have been implicated as risk factors for transfusion-related acute lung injury.[32,33] Another limitation to our study is the lack of brain imaging or transcranial Doppler data in the enrolled patients; therefore, we are left to speculate that a higher embolic load may have contributed to the cognitive decline. Finally, 21% of our baseline population did not return for follow-up testing. As expected, nonreturning patients were sicker (worse Charlson comorbidity score) than returnees; however, the other demographic characteristics listed in table 2 were not different, and the rate of loss to follow-up was not different between the two treatment groups.

In summary, this trial is the first to evaluate the effect of hemodilution on neurocognitive outcomes after adult cardiac surgery in a prospective randomized manner. Because of an increase in adverse events in patients randomized to a higher hematocrit level, this study was terminated early. Despite the incomplete enrollment, we report that older patients experiencing profound hemodilution were more likely to experience cognitive decline. Our results suggest that both extreme hemodilution in the elderly and aggressive transfusion should be used with caution in the management of CPB during cardiac surgery.

References

1. Cook DJ, Orszulak TA, Daly RC: Minimum hematocrit at differing cardiopulmonary bypass temperatures in dogs. Circulation 1998; 98:II170–4
2. Cook DJ, Orszulak TA, Daly RC, MacVeigh I: Minimum hematocrit for normothermic cardiopulmonary bypass in dogs. Circulation 1997; 96:II-200–4
3. Reasoner DK, Ryu KH, Hindman BJ, Cutkomp J, Smith T: Marked hemodilution increases neurologic injury after focal cerebral ischemia in rabbits. Anesth Analg 1996; 82:61–7
4. Lee SH, Heros RC, Mullan JC, Korosue K: Optimum degree of hemodilution for brain protection in a canine model of focal cerebral ischemia. J Neurosurg 1994; 80:469–75
5. Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, Mark DB, Reves JG, Blumenthal JA: Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med 2001; 344:395–402
6. Phillips-Bute B, Mathew JP, Blumenthal JA, Grocott HP, Laskowitz DT, Jones RH, Mark DB, Newman MF: Association of neurocognitive function and quality of life 1 year after coronary artery bypass graft (CABG) surgery. Psychosom Med 2006; 68:369–75
7. DeFoe GR, Ross CS, Olmstead EM, Surgenor SD, Fillinger MP, Groom RC, Forest RJ, Pieroni JW, Warren CS, Bogosian ME, Krumholz CF, Clark C, Clough RA, Weldner PW, Lahey SJ, Leavitt BJ, Marrin CA, Charlesworth DC, Marshall P, O'Connor GT: Lowest hematocrit on bypass and adverse outcomes associated with coronary artery bypass grafting. Northern New England Cardiovascular Disease Study Group. Ann Thorac Surg 2001; 71:769–76
8. Fang WC, Helm RE, Krieger KH, Rosengart TK, DuBois WJ, Sason C, Lesser ML, Isom OW, Gold JP: Impact of minimum hematocrit during cardiopulmonary bypass on mortality in patients undergoing coronary artery surgery. Circulation 1997; 96:II-194–9
9. Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ, Shah A: Adverse effects of low hematocrit during cardiopulmonary bypass in the adult: Should current practice be changed? J Thorac Cardiovasc Surg 2003; 125:1438–50
10. Karkouti K, Beattie WS, Wijeysundera DN, Rao V, Chan C, Dattilo KM, Djaiani G, Ivanov J, Karski J, David TE: Hemodilution during cardiopulmonary bypass is an independent risk factor for acute renal failure in adult cardiac surgery. J Thorac Cardiovasc Surg 2005; 129:391–400
11. Karkouti K, Djaiani G, Borger MA, Beattie WS, Fedorko L, Wijeysundera D, Ivanov J, Karski J: Low hematocrit during cardiopulmonary bypass is associated with increased risk of perioperative stroke in cardiac surgery. Ann Thorac Surg 2005; 80:1381–7
12. Harrell FE: Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis. New York, Springer, 2001
13. Cole DJ, Drummond JC, Patel PM, Reynolds LR: Hypervolemic-hemodilution during cerebral ischemia in rats: Effect of diaspirin cross-linked hemoglobin (DCLHb) on neurologic outcome and infarct volume. J Neurosurg Anesthesiol 1997; 9:44–50
14. Belayev L, Busto R, Zhao W, Clemens JA, Ginsberg MD: Effect of delayed albumin hemodilution on infarction volume and brain edema after transient middle cerebral artery occlusion in rats. J Neurosurg 1997; 87:595–601
15. Homi HM, Yang H, Pearlstein RD, Grocott HP: Hemodilution during cardiopulmonary bypass increases cerebral infarct volume after middle cerebral artery occlusion in rats. Anesth Analg 2004; 99:974–81
16. Jonas RA, Wypij D, Roth SJ, Bellinger DC, Visconti KJ, du Plessis AJ, Goodkin H, Laussen PC, Farrell DM, Bartlett J, McGrath E, Rappaport LJ, Bacha EA, Forbess JM, del Nido PJ, Mayer JE Jr, Newburger JW: The influence of hemodilution on outcome after hypothermic cardiopulmonary bypass: Results of a randomized trial in infants. J Thorac Cardiovasc Surg 2003; 126:1765–74
17. Harrison MJ, Stygall J, Whitaker DC, Grundy NM, Newman SP: Hematocrit during cardiopulmonary bypass. Ann Thorac Surg 2006; 82:1166
18. Weiskopf RB, Kramer JH, Viele M, Neumann M, Feiner JR, Watson JJ, Hopf HW, Toy P: Acute severe isovolemic anemia impairs cognitive function and memory in humans. ANESTHESIOLOGY 2000; 92:1646–52
19. Weiskopf RB, Toy P, Hopf HW, Feiner J, Finlay HE, Takahashi M, Bostrom A, Songster C, Aminoff MJ: Acute isovolemic anemia impairs central processing as determined by P300 latency. Clin Neurophysiol 2005; 116:1028–32
20. Cook DJ, Oliver WC Jr, Orszulak TA, Daly RC, Bryce RD: Cardiopulmonary bypass temperature, hematocrit, and cerebral oxygen delivery in humans. Ann Thorac Surg 1995; 60:1671–7
21. Sungurtekin H, Cook DJ, Orszulak TA, Daly RC, Mullany CJ: Cerebral response to hemodilution during hypothermic cardiopulmonary bypass in adults. Anesth Analg 1999; 89:1078–83
22. Pugsley W, Klinger L, Paschalis C, Treasure T, Harrison M, Newman S: The impact of microemboli during cardiopulmonary bypass on neuropsychological functioning. Stroke 1994; 25:1393–9
23. Hammon JW Jr, Stump DA, Kon ND, Cordell AR, Hudspeth AS, Oaks TE, Brooker RF, Rogers AT, Hilbawi R, Coker LH, Troost BT: Risk factors and solutions for the development of neurobehavioral changes after coronary artery bypass grafting. Ann Thorac Surg 1997; 63:1613–8
24. Jacobs A, Neveling M, Horst M, Ghaemi M, Kessler J, Eichstaedt H, Rudolf J, Model P, Bonner H, de Vivie ER, Heiss WD: Alterations of neuropsychological function and cerebral glucose metabolism after cardiac surgery are not related only to intraoperative microembolic events. Stroke 1998; 29:660–7
25. Sungurtekin H, Plochl W, Cook DJ: Relationship between cardiopulmonary bypass flow rate and cerebral embolization in dogs. ANESTHESIOLOGY 1999; 91:1387–93
26. Hill SE, Grocott HP, Leone BJ, White WD, Newman MF: Cerebral physiology of cardiac surgical patients treated with the perfluorocarbon emulsion, AF0144. Ann Thorac Surg 2005; 80:1401–7
27. Li M, Ratcliffe SJ, Knoll F, Wu J, Ances B, Mardini W, Floyd TF: Aging: Impact upon local cerebral oxygenation and blood flow with acute isovolemic hemodilution. J Neurosurg Anesthesiol 2006; 18:125–31
28. Floyd TF, McGarvey M, Ochroch EA, Cheung AT, Augoustides JA, Bavaria JE, Acker MA, Pochettino A, Detre JA: Perioperative changes in cerebral blood flow after cardiac surgery: Influence of anemia and aging. Ann Thorac Surg 2003; 76:2037–42
29. van de Watering LM, Hermans J, Houbiers JG, van den Broek PJ, Bouter H, Boer F, Harvey MS, Huysmans HA, Brand A: Beneficial effects of leukocyte depletion of transfused blood on postoperative complications in patients undergoing cardiac surgery: A randomized clinical trial. Circulation 1998; 97:562–8

30. Leal-Noval SR, Marquez-Vacaro JA, Garcia-Curiel A, Camacho-Larana P, Rincon-Ferrari MD, Ordonez-Fernandez A, Flores-Cordero JM, Loscertales-Abril J: Nosocomial pneumonia in patients undergoing heart surgery. Crit Care Med 2000; 28:935–40

31. Leal-Noval SR, Rincon-Ferrari MD, Garcia-Curiel A, Herruzo-Aviles A, Camacho-Larana P, Garnacho-Montero J, Amaya-Villar R: Transfusion of blood components and postoperative infection in patients undergoing cardiac surgery. Chest 2001; 119:1461–8

32. Silliman CC, Boshkov LK, Mehdizadehkashi Z, Elzi DJ, Dickey WO, Podlosky L, Clarke G, Ambruso DR: Transfusion-related acute lung injury: Epidemiology and a prospective analysis of etiologic factors. Blood 2003; 101:454–62

33. Silliman CC, Ambruso DR, Boshkov LK: Transfusion-related acute lung injury. Blood 2005; 105:2266–73

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