Hemodilution and Hematocrit: How Low Do You Go?

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The advent of hypothermic cardiopulmonary bypass (CPB) has made intentional hemodilution a standard practice, as 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 lowered to hematocrit values <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 Physiologically important changes in cerebral oxygen supply were however reported in subsets of the animals at hematocrits as high as 18%.1 Limits to hemodilution were also suggested by other animal data3, 4 but, in general, the consequences of extreme hemodilution, a common clinical practice during CPB, were largely unknown.

The deleterious consequences of extreme hemodilution during CPB in humans have been recently 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 al5 studying 10,949 patients undergoing cardiac surgery with CPB reported a 10% increase in the odds of suffering a perioperative stroke with each percent decrease in hematocrit. (Figure 1) Potential mechanisms for this injury include increased cerebral embolic load and diminished oxygen delivery to ischemic areas of the brain. 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 <21% (Figure 2).6 Interestingly, the odds of developing renal failure was also increased in those with a hematocrit >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 mortality7, 8 (Figure 3) and reduced survival up to 6 years after surgery.9

Prospective randomized trials assessing hemodilution, however, are scarce. 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. The lower hematocrit group had lower nadirs of cardiac index, higher serum lactate levels 60 minutes after CPB, and at age 1 year, had worse scores on a psychomotor development index. To further assess the effects of hemodilution upon cognition, we randomized patients undergoing coronary artery bypass grafting surgery to either moderate hemodilution (MH: hematocrit on cardiopulmonary bypass ≥ 27%) or profound hemodilution (PH: 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. 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 mmHg compared to 52.4 ± 5.2 mmHg in the PH group (p=0.11). The mean volume of blood removed in the PH group prior to the onset of CPB was 1578 ml [IQR: 640-2000]. Eighty nine percent of the MH patients were transfused with homologous blood products compared to 88% of the PH patients (p = 0.86). Intra- and postoperatively, the MH group received a median of 900 ml [IQR: 600-1500] PRBC compared to 900 ml [IQR: 600-1900]; (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 standard deviation or more in performance on at least 1 of the 4 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 suffer cognitive decline (binary outcome: p = 0.03; continuous outcome: p = 0.02). 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). In an attempt to determine if 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% vs. 19.9 ± 4.6% in the PH group (p<0.001). Once 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. To investigate the possibility of a non-linear association between hematocrit drop and cognitive change, an analysis using restricted
cubic splines was performed in the subset of patients who were ≥70 years old. 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 tails, can greatly improve the fit of the model. Figure 4 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 percentage points.

The effects of hemodilution during CPB on ischemic neurological 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,11,12 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 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.2 Subsequent study by these same investigators 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 38ºC, 28ºC, and 18ºC, respectively.1 Limits to the extent of hemodilution were also described by Lee and colleagues 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%.4 Similarly, Reasoner et al5 found an increase in hemispheric infarct size after middle cerebral artery occlusion in rabbits when marked hemodilution (hematocrit = 18%) was employed. More recently, Homi et al13 also hemodiluted rats surgically prepared for CPB to a hematocrit of 18% and reported both worsened functional neurological performance and greater cerebral infarct volumes 24 hours after middle cerebral artery occlusion, when compared to control animals maintained at a hematocrit of 33%.

Acute isovolumic anemia to a hematocrit of 15-18% in healthy volunteers has been reported to increase reaction time and degrade immediate and delayed memory during cognitive testing.14 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.15 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 if 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 and colleagues, 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. As 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. Pathological and Doppler studies 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. 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 relationship 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. 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.

How low should you go? Available data from many retrospective and a few prospective studies suggest that a nadir hematocrit < 20-21% is associated with greater renal failure, stroke, cognitive decline, and short and long-term mortality. Thus, it would be prudent to avoid profound hemodilution during CPB, particularly in the elderly. However, it should be noted that transfusion has also been associated with many of these same risks and aggressive transfusion should also be used with caution in the management of CPB during cardiac surgery.

References: