Hemodilution during cardiopulmonary bypass is an independent risk factor for acute renal failure in adult cardiac surgery

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Background: This observational study sought to determine whether the degree of hemodilution during cardiopulmonary bypass is independently related to perioperative acute renal failure necessitating dialysis support.

Methods: Data were prospectively collected on consecutive patients undergoing cardiac operations with cardiopulmonary bypass from 1999 to 2003 at a tertiary care hospital. The independent relationship was assessed between the degree of hemodilution during cardiopulmonary bypass, as measured by nadir hematocrit concentration, and acute renal failure necessitating dialysis support. Multivariate logistic regression was used to control for variables known to be associated with perioperative renal failure and anemia.

Results: Of the 9080 patients included in the analysis, 1.5% (n = 134) had acute renal failure necessitating dialysis support. There was an independent, nonlinear relationship between nadir hematocrit concentration during cardiopulmonary bypass and acute renal failure necessitating dialysis support. Moderate hemodilution (nadir hematocrit concentration, 21%-25%) was associated with the lowest risk of acute renal failure necessitating dialysis support; the risk increased as nadir hematocrit concentration deviated from this range in either direction ($P = .005$). Compared with moderate hemodilution, the adjusted odds ratio for acute renal failure necessitating dialysis support with severe hemodilution (nadir hematocrit concentration <21%) was 2.34 (95% confidence interval, 1.47-3.71), and for mild hemodilution (nadir hematocrit concentration >25%) it was 1.88 (95% confidence interval, 1.02-3.46).

Conclusions: Given that there is an independent association between the degree of hemodilution during cardiopulmonary bypass and perioperative acute renal failure necessitating dialysis support, patient outcomes may be improved if the nadir hematocrit concentration during cardiopulmonary bypass is kept within the identified optimal range. Randomized clinical trials, however, are needed to determine whether this is a cause-effect relationship or simply an association.

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This study examined the relationship between the degree of hemodilution during cardiopulmonary bypass (CPB) in cardiac operations and postoperative acute renal failure (ARF) necessitating dialysis support (ARF-D). Renal failure necessitating dialysis support is a devastating complication of cardiac surgery: it occurs in 1% to 5% of patients and is strongly associated with serious adverse events, including death.¹⁻³

The current practice of CPB, which entails the addition of 1.5 to 2 L or more of nonhematic fluids (crystalloid and colloid fluids used to prime the CPB circuit) to the patient's blood volume, frequently results in marked hemodilution, often to hematocrit concentrations less than 20%. This practice, which is in contrast to the early days of cardiac surgery, when allogeneic blood was used as a prime to avoid hemodilution, was adapted primarily to reduce the use of blood products.⁴ Although this practice has now been accepted for more than 4 decades, there is a renewed debate about the optimal degree of hemodilution during CPB.^{5,6} Recent studies have found a direct association between the severity of hemodilution during CPB and perioperative morbidity and mortality.⁶⁻⁹ More specifically, there is a growing body of evidence linking low hematocrit concentrations during CPB with an increased risk of renal dysfunction.^{6,10,11} Earlier evidence, however, suggested that hemodilution confers protection against renal injury.^{12,13}

Although seemingly contradictory, these findings may be congruent if the relationship between the degree of hemodilution during CPB and post-cardiac operation ARF is more U-shaped than linear. Hematocrit concentrations at the trough of the curve would confer the lowest risk of renal dysfunction, with the risk increasing as the hematocrit deviates from this optimal concentration in either direction. The objective of this study was to determine whether such an optimal hematocrit concentration exists by assessing the relationship between nadir hematocrit concentration (nHct) during CPB and postoperative ARF-D while controlling for multiple perioperative variables known to be related to perioperative renal dysfunction and anemia. Such a finding would be important for it would suggest a means of protecting the kidneys against injury during cardiac operations.

Methods

After institutional ethics approval, data on consecutive adult (≥ 18 years) patients undergoing cardiac operation with CPB at the Toronto General Hospital from June 1999 to June 2003 were identified from a prospectively collected database, the details of which have been previously described.^{14,15} A full-time research nurse, who was blinded to the details of this study and to the intraoperative hematocrit data, adjudicated all outcomes from patients' medical records. Attending anesthesiologists, surgeons, and perfusionists collected all preoperative and intraoperative data,

with the exception of blood-product transfusion data. A research assistant obtained the transfusion data from the transfusion laboratory's database (Hemocare, Mediware Information Systems, Melville, NY).

Study Setting and Clinical Practice

The Toronto General Hospital is a tertiary care teaching hospital affiliated with the University of Toronto. A full range of adult cardiac surgery procedures, including such complex procedures as congenital heart disease repair and heart transplantation, is performed at this hospital.

During the study period, patients were managed according to standardized clinical protocols as described below.

Anesthetic management. Fast-track anesthesia with fentanyl (10-20 $\mu\text{g/kg}$), midazolam (0.1 mg/kg), pancuronium (0.15-0.20 mg/kg), isoflurane (0.5%-1.5%), and propofol (0.5-4 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) was used. Patients were routinely monitored with pulmonary artery catheters. Transesophageal echocardiography was routinely used except for patients undergoing isolated aortocoronary bypass. Epiaortic scanning was not routinely used. Antifibrinolytic drugs—tranexamic acid (50-100 mg/kg) or aprotinin (6×10^6 U), depending on bleeding risk—were used prophylactically in every patient undergoing CPB.

CPB management. Anticoagulation was achieved with heparin to maintain an activated clotting time more than 480 seconds. The CPB circuit was primed with 1.8 L of lactated Ringer's solution and 50 mL of 20% mannitol. Albumin (25%) and synthetic colloids (Pentaspan; Bristol-Myers Squibb Canada Inc, Montreal, Quebec, Canada) were added to the circuit as needed. Management of CPB included systemic temperature drift to 34°C, alpha-stat pH management, targeted mean perfusion pressure between 50 and 70 mm Hg, and pump flow rates of 2.0 to 2.4 $\text{L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$. Myocardial protection was achieved with intermittent antegrade and, occasionally, retrograde blood cardioplegia. When necessary, deep hypothermic circulatory arrest (DHCA) was achieved by cooling to 20°C with or without retrograde cerebral perfusion. Furosemide was administered in response to persistent oliguria or hyperkalemia.

During CPB, red blood cell concentrate (leukoreduced allogeneic or autologous) was transfused to maintain the hematocrit concentration more than 17%. Pericardial blood was salvaged into the cardiomy suction reservoir and was reinfused via the CPB circuit as long as patients were anticoagulated. After separation from CPB, heparin was neutralized with protamine sulphate, 1 mg per 100 U of heparin, to achieve an activated clotting time within 10% of baseline. After CPB, red blood cell concentrate was transfused to maintain the hematocrit more than 21% to 24% in stable patients and more than 27% in bleeding or unstable patients.

Dependent Variable

ARF was defined as a new requirement for postoperative dialysis.

Independent Variables

The primary variable of interest was nHct during CPB. Variables that may be related to perioperative renal dysfunction^{1-3,16} or anemia^{15,17,18} were considered for inclusion in the multivariate analysis as confounding variables (Table 1).

TABLE 1. Bivariate relationship of independent variables with ARF-D

	ARF-D	No ARF-D	P Value
Preoperative patient variables			
Age, y (mean $\pm$ SD)	64 $\pm$ 14	62 $\pm$ 12	.2
Sex			
Male	90 (1.3%)	6708	.04
Female	44 (1.9%)	2238	
Height, cm (mean $\pm$ SD)	167 $\pm$ 11	169 $\pm$ 11	.07
Weight, kg (mean $\pm$ SD)	74 $\pm$ 17	79 $\pm$ 16	<.001
Hypertension			
No	59 (1.4%)	4140	.6
Yes	75 (1.5%)	4806	
Diabetes mellitus			
No	81 (1.2%)	6693	<.001
Yes	53 (2.3%)	2253	
Peripheral vascular disease (history of aortoiliac, femoropopliteal, or carotid disease or operation)			
No	104 (1.3%)	7715	.004
Yes	30 (2.4%)	1231	
Cerebrovascular disease (history of stroke or transient ischemic attacks)			
No	116 (1.4%)	8134	.07
Yes	18 (2.2%)	812	
Hyperlipidemia (on treatment at time of operation)			
No	62 (1.8%)	3402	.06
Yes	72 (1.3%)	5544	
Smoker at time of operation			
No	60 (1.9%)	3145	.02
Yes	74 (1.3%)	5801	
Chronic obstructive pulmonary disease			
No	126 (1.5%)	8013	.09
Yes	8 (0.8%)	933	
Atrial fibrillation			
No	111 (1.3%)	8391	<.001
Yes	23 (4.0%)	555	
New York Heart Association class			
I or II	12 (0.5%)	2483	<.001
III or IV	122 (1.8%)	6463	
Left ventricular ejection fraction			
$\geq 40\%$	84 (1.2%)	7149	<.001
<40%	50 (2.7%)	1797	
Unstable angina (within 30 d of operation)			
No	73 (1.6%)	5140	.6
Yes	61 (1.4%)	3806	
Recent myocardial infarction (within 30 d of operation)			
No	109 (1.4%)	7519	.4
Yes	25 (1.7%)	1427	
Recent cardiac catheterization (within 2 d of operation)			
No	103 (1.3%)	8054	<.001
Yes	31 (3.3%)	892	
Congestive heart failure (at time of operation)			
No	54 (0.8%)	7083	<.001
Yes	80 (4.2%)	1863	
Shock (at time of operation)			
No	119 (1.3%)	8831	<.001
Yes	15 (11.4%)	115	

TABLE 1. Continued

	ARF-D	No ARF-D	P Value
Endocarditis (at time of operation)			
No	132 (1.5%)	8877	.4
Yes	2 (2.8%)	69	
Intra-aortic balloon pump (inserted before operation)			
No	121 (1.4%)	8726	<.001
Yes	13 (5.6%)	220	
Renal function (creatinine; $\mu\text{mol/L}$; abnormal >100 in women; >110 in men)			
Normal	54 (0.7%)	7270	<.001
Abnormal	80 (4.6%)	1676	
Severe renal dysfunction (creatinine; $\mu\text{mol/L}$; >200 in women; >220 in men)			
No	117 (1.3%)	8912	<.001
Yes	17 (33.3%)	34	
Hemoglobin concentration, g/dL (mean $\pm$ SD)	12 $\pm$ 2	13 $\pm$ 1.5	<.001
Preoperative operative variables			
Urgency			
Elective	88 (1.1%)	8252	<.001
Urgent	46 (6.2%)	694	
Repeat surgery			
No	110 (1.3%)	8236	<.001
Yes	24 (3.3%)	710	
Procedure (for multivariate analysis, ACB and single valve were combined)			
ACB	52 (0.9%)	5835	
Single valve	8 (0.9%)	895	<.001
Other (complex)	74 (3.3%)	2216	
Intraoperative variables			
Lowest hematocrit during CPB, % (mean $\pm$ SD)	21 $\pm$ 4	23 $\pm$ 4	<.001
Highest blood glucose during CPB, mmol/L (mean $\pm$ SD)	15.8 $\pm$ 5.0	14.2 $\pm$ 3.9	<.001
Lowest mean arterial pressure during CPB, mm Hg (mean $\pm$ SD)	49 $\pm$ 10	48 $\pm$ 10	.1
CPB duration, min (mean $\pm$ SD)	143 $\pm$ 72	100 $\pm$ 37	<.001
Deep hypothermic circulatory arrest			
No	124 (1.4%)	8653	.01
Yes	10 (3.3%)	293	
RBC transfusion on the day of operation			
No	26 (0.5%)	5056	<.001
Yes	108 (2.7%)	3890	
Excessive perioperative blood loss (≥ 5 U of RBC transfused on the day of operation)			
No	78 (0.9%)	8213	<.001
Yes	56 (7.1%)	733	
Post-CPB variables			
Difficult wean from CPB (requirement for inotropes or intra-aortic balloon pump)			
No	42 (0.5%)	7763	<.001
Yes	92 (7.2%)	1183	
Re-exploration			
No	90 (1.1%)	8434	<.001
Yes	44 (7.9%)	512	

TABLE 1. Continued

	ARF-D	No ARF-D	P Value
Low-output syndrome (use of inotropes or mechanical devices for >30 min to maintain blood pressure >90 mm Hg with a cardiac index <2.2 L · min ⁻¹ · m ⁻²)			
No	79 (0.9%)	8606	<.001
Yes	55 (14.0%)	340	
Adverse events (any of the following: arrhythmias requiring treatment, myocardial infarction, pulmonary complications, stroke, sepsis)			
No	26 (0.4%)	6021	<.001
Yes	108 (3.6%)	2925	

ARF-D, Acute respiratory failure necessitating dialysis; ACB, aortocoronary bypass; CPB, cardiopulmonary bypass; RBC, red blood cell concentrate.

Statistical Analysis

SAS version 8.2 (SAS Institute Inc, Cary, NC) was used for statistical analyses. Database accuracy was measured by comparing all outlying values with patients' records and by reabstracting the medical records of 200 randomly selected patients. Whenever possible, missing values were completed from patients' records; otherwise, patients with missing categorical variable or nHct values were excluded. For continuous variables other than nHct, missing values were imputed on the basis of the mean, according to postoperative renal status, for the entire sample. Patients requiring preoperative dialysis support were excluded from analysis.

The bivariate associations between the independent variables and ARF-D were assessed by using appropriate tests (*t* test, Mann-Whitney *U* test, χ^2 test, Fisher exact test, or Mantel-Haenszel test). The bivariate associations between nHct and other independent variables were assessed by the Pearson correlation test. Variables that were associated ($P \leq 0.1$) with both ARF-D and nHct were included in the logistic regression analysis.

The mathematical relationships between the continuous independent variables and the probability of ARF-D (logit transformation) were assessed with restricted cubic spline functions.¹⁹⁻²¹ Variables that were not linearly related were either mathematically transformed or categorized for the logistic regression analysis.²² A Pearson correlation matrix was used to identify collinear independent variables.²²

Two logistic regression models were constructed that controlled for all identified confounders (for correlated variables, only the most predictive was included in the multivariable analysis) with ARF-D as the dependent variable. In model 1, nHct was included in its quadratic form (nHct – sample mean of nHct)² in addition to its untransformed form to compensate for its nonlinear relationship with ARF-D (as identified by the cubic spline function analysis).²² In model 2, nHct was categorized into 3 hemodilution groups: mild (nHct >25%), moderate (nHct 21%-25%), and severe (nHct <21%). These cutoffs were defined by the 25th and 75th nHct percentiles. Each group was treated as a separate, independent variable in the logistic regression analysis.²² In sensitivity analyses, the robustness of the association between nHct and ARF-D was assessed by repeating model 2's regression analysis in 2 different subgroups: (1) excluding patients who had severe baseline renal dysfunction (defined as creatinine concentration more than twice the upper limit of normal) and were therefore

at the highest risk for development of ARF-D and (2) including only patients who underwent isolated aortocoronary bypass (by providing a homogeneous patient population, this subgroup analysis removes many confounding issues, such as operative complexity, DHCA, and antifibrinolytic use). All models were constructed by using backward stepwise variable selection with $P \leq .05$ as the criterion for variable retention. The models' fit was assessed by the Hosmer-Lemeshow (goodness-of-fit) test (a larger *P* value means better fit or reliability),²³ and predictive accuracy was assessed by the c-index (which is equivalent to the area under the receiver operating characteristic [ROC] curve; an area of 0.5 indicates no predictive discrimination and an area of 1.0 indicates perfect separation of patients with different outcomes).²⁴

To explore the effects of risk adjustment on the association between nHct and ARF-D, the distributions of the other independent predictors of ARF-D (covariates in model 2) were obtained for each of the hemodilution groups. The bootstrap technique²⁵ was used to assess validity of model 2 as follows: 100 computer-generated samples, each including 9000 patients, were derived from the study population by random selection with replacement. For each sample, model 2 was refitted, and the confidence intervals (CIs) for the coefficients of the nHct categories were obtained.

Results

During the study period, 9215 patients underwent cardiac operations with CPB. Fifty-seven patients were readmitted for additional operations necessitating CPB; only data from the first operation were used (ARF-D developed in none after either operation). Forty-seven patients with missing data and 88 patients with preexisting renal failure necessitating dialysis were excluded, leaving a total of 9080 patients for analysis. Database accuracy was more than 95%.

The mortality rate was 1.7% (*n* = 150); the ARF-D rate was 1.5% (*n* = 134). The unadjusted relationships between ARF-D and the independent variables, including nHct as a continuous variable, are shown in Table 1. Figure 1 shows the spline function graph of the relationship between nHct and ARF-D. On the basis of the shape of this relationship, nHct was categorized as previously described into mild (>25%), moderate (21%-25%), and severe (<21%) he-

Figure 1. Estimated spline transformation and 95% confidence interval for nadir CPB hematocrit and acute renal failure necessitating dialysis (ARF-D).

modulation groups. The unadjusted relationship between ARF-D and nHct is presented in Figure 2.

The following baseline variables were associated with ARF-D and nHct by bivariate analysis: sex, weight, diabetes, peripheral vascular disease, cerebrovascular disease, atrial fibrillation, left ventricular ejection fraction, recent cardiac catheterization, shock, renal function, and hemoglobin concentration. The following intraoperative and postoperative variables were also associated: urgency, procedure type, highest blood glucose during CPB, DHCA, excessive perioperative blood loss, difficult wean from CPB, re-exploration, low output syndrome, and serious adverse events. These variables, as well as age and CPB duration, were included in the logistic regression analysis.

In models 1 and 2, nHct was independently associated with ARF-D. In model 1, which included the quadratic form of nHct, the risk of ARF-D was increased as nHct deviated from the mean nHct of 23% ($P = .005$). The model was reliable (Hosmer-Lemeshow test, $P = .5$) and discriminative (c-index, 0.94). When nHct was included as 3 categorical variables, moderate hemodilution (nHct, 21%-25%) was associated with the lowest risk of ARF-D. Compared with moderate hemodilution, the odds ratio for ARF-D with severe hemodilution (nHct <21%) was 2.34 (95% CI, 1.47-3.71), and for mild hemodilution (nHct >25%) it was 1.88 (95% CI, 1.02-3.46). This model, which is presented in Table 2, was also reliable (Hosmer-Lemeshow test, $P = .4$) and discriminative (c-index, 0.94). The sensitivity analyses (Table 3) showed the adjusted odds ratio for ARF-D to be stable in the 2 patient subsets analyzed. The risk estimate for the mild-hemodilution group, however, was not as robust as the estimate for the severe-hemodilution group. Table 4

outlines the risk profile of the hemodilution groups in terms of the independent predictors of ARF-D (covariates in model 2). In all 100 bootstrap samples, nHct remained in the logistic regression model, with the 95% CI of the coefficients within $\pm 2\%$ of those in model 2.

Discussion

This study found that the degree of hemodilution during CPB, as measured by nHct, was independently related to the risk of ARF-D. After adjustment for multiple potential confounders, moderate hemodilution (nHct, 21%-25%) was associated with the lowest risk of ARF-D, with the odds of ARF-D 2.34 times (95% CI, 1.47-3.71) higher with severe hemodilution (nHct <21%) and 1.88 times (95% CI, 1.02-3.46) higher with mild hemodilution (nHct >25%).

These adjusted odds ratios were markedly different from the unadjusted relationship between nHct and ARF-D (Figure 2). Adjustment for confounders reduced the risk of severe hemodilution and increased the risk of mild hemodilution relative to moderate hemodilution. This occurs because patients in the mild-hemodilution group have the most favorable risk profile and those in the severe-hemodilution group have the least favorable risk profile. The actual risk of ARF-D that is attributable to nHct, therefore, becomes evident only after these risk differences are accounted for by multivariate analysis.

The observed association between the degree of hemodilution during CPB and ARF-D is biologically plausible and is supported by existing literature. According to postmortem findings, the 2 most common etiologies for ARF after CPB are acute tubular necrosis caused by inadequate oxygen delivery and renal infarction caused, presumably, by micro-

Figure 2. A, Unadjusted relationship between nadir CPB hematocrit and acute renal failure necessitating dialysis (ARF-D). B, Incidence of ARF-D in categories of nadir CPB hematocrit.

emboli.^{26,27} The degree of hemodilution during CPB affects both renal oxygen delivery and renal embolic load.

Hemodilution and Renal Oxygen Delivery

Progressive hemodilution causes a proportional decrease in the oxygen-carrying capacity of the blood. As blood becomes more dilute, however, it also becomes less viscous, leading to increased blood flow in the macrocirculation and microcirculation.^{28,29} This increased flow compensates for the decreased oxygen-carrying capacity of blood, but only to an as-yet-undefined “critical” hematocrit concentration beyond which further hemodilution results in reduced tissue

oxygen delivery.³⁰ In vitro studies have found that even slight reductions in renal oxygen delivery can cause ischemic injury in certain highly susceptible areas of the kidney, especially if the kidney’s energy requirements are increased.^{31,32} Hematocrit concentrations below this critical level would therefore place susceptible areas of the kidney at risk for ischemic injury. Further aggravating this risk may be the increased renal blood flow that occurs in response to hemodilution, which may increase the energy requirements of the kidney for tubular transport work by increasing renal perfusion and the glomerular filtration rate.^{31,33} Yet another aggravating factor is the proportional reduction in plasma oncotic pressure

TABLE 2. Variables independently related to ARF-D: Results of the logistic regression model in which nadir hematocrit during CPB (nHCT) was included as 3 categorical variables

Variable	Coefficient	SE	Odds ratio	95% CI
Intercept	1.14	3.94		
Preoperative variables				
Diabetes mellitus (yes vs no)	0.74	0.21	2.1	1.4–3.1
Atrial fibrillation (yes vs no)	0.88	0.29	2.4	1.4–4.2
Renal function (abnormal vs normal)	1.46	0.20	4.3	2.9–6.4
Baseline hemoglobin (continuous; log trans)	−1.9	0.80	0.15	0.03–0.7
Urgency (urgent vs elective)	0.83	0.23	2.3	1.5–3.6
Procedure				
Complex vs isolated ACB or single valve	0.70	0.21	2.0	1.3–3.1
Intraoperative variables				
nHCT during CPB				
<21% vs 21%–25%	0.35	0.16	2.34	1.47–3.71
>25% vs 21%–25%	0.14	0.19	1.88	1.02–3.46
Post-CPB variables				
CPB weaning problems (yes vs no)	1.13	0.23	3.1	2.0–4.8
Re-exploration (yes vs no)	1.32	0.22	3.7	2.4–5.8
Low-output syndrome (yes vs no)	1.33	0.23	3.8	2.4–5.9
Adverse events (yes vs no)	1.66	0.24	5.2	3.3–8.3

Hosmer-Lemeshow goodness-of-fit test = 0.4; c-index = 0.944. *CI*, Confidence interval; *ACB*, aortocoronary bypass; *CPB*, cardiopulmonary bypass.

TABLE 3. Sensitivity analyses*

Sample	nHct	Odds ratio	95% CI
Excluding patients with severe preoperative renal dysfunction	<21% vs 21%–25%	2.2	1.4–3.6
	>25% vs 21%–25%	1.6	0.9–2.9
Including only patients who underwent isolated ACB	<21% vs 21%–25%	3.4	1.7–6.8
	>25% vs 21%–25%	1.3	0.4–4.1

nHct, Nadir hematocrit concentration; *CI*, confidence interval; *ACB*, aortocoronary bypass.

*Both models were developed by using the same strategy as model 2 (refer to text).

that occurs with hemodilution. This results in the accumulation of fluid in the interstitial space, which may ultimately lead to capillary closure and reduced tissue oxygen delivery.^{4,28,30}

Hemodilution and Renal Embolic Load

The conduct of CPB generates a large number of emboli of various origins.^{34,35} The increase in renal blood flow associated with hemodilution may increase the relative number of emboli flowing to the kidneys, thereby increasing the risk of renal infarction and ARF.

These pathophysiological mechanisms provide an explanation for this study's finding that severe hemodilution is associated with a higher risk of ARF-D than is moderate

hemodilution. This finding is also supported by other observational studies that have found a direct relationship between the severity of hemodilution and increasing risk of renal, hepatic, and central nervous system dysfunction, as well as mortality.^{6–11}

The other finding of this study, that mild hemodilution may be associated with a higher risk of ARF-D than moderate hemodilution, is equally plausible. Hemodilution during CPB reduces red blood cell injury,²⁹ an important cause of renal dysfunction.^{27,36} Furthermore, hemodilution prevents the deleterious trapping of red blood cells that occurs in the renal microvasculature after renal ischemia.^{12,13} Through these mechanisms, as well as by improving microcirculatory blood flow as described previously, moderate hemodilution may therefore confer more protection than mild hemodilution against ischemic renal injury. In contrast to this study, however, previous observational studies in cardiac surgery did not find an increased risk of renal dysfunction with mild compared with moderate hemodilution.^{6,11} This discrepancy may be due to differences in the definition of ARF, sample size, study population, distribution of nHct, or statistical analyses. Of note, this study's estimated association between ARF-D and mild versus moderate hemodilution was not as robust as that for severe versus moderate hemodilution, as is evident by the 95% CIs in both the primary (Table 2) and sensitivity (Table 3) analyses.

Several steps were taken in this study to ensure that the results were a valid estimate of the "true" relationship

TABLE 4. Risk profile of the hemodilution groups with respect to covariates in model 2

Covariate	Severe hemodilution	Moderate hemodilution	Mild hemodilution
Diabetes	30.2%	25.3%	20.2%
Atrial fibrillation	4.9%	6.4%	7.8%
Renal dysfunction	24.2%	19.0%	14.7%
Baseline hemoglobin, g/dL (mean $\pm$ SD)	12.2 $\pm$ 1.4	13.5 $\pm$ 1.3	14.6 $\pm$ 1.1
Nonelective procedure	13.2%	6.6%	5.9%
Complex procedure	23.5%	23.6%	30.7%
CPB weaning problems	20.8%	12.3%	10.2%
Re-exploration	7.4%	5.7%	5.8%
Low-output syndrome	8.6%	3.4%	1.9%
Adverse events	36.5%	33.2%	30.6%

CPB, Cardiopulmonary bypass.

between nHct during CPB and renal dysfunction. First, a clear and relevant measure of renal dysfunction—the need for dialysis—was used, as opposed to a surrogate measure, such as change in serum creatinine.³⁷ Second, a prospectively collected and accurate database was used. Third, multiple confounders were identified and adjusted for, including several measures of severity of illness, intraoperative stability, surgical complexity, and perioperative complications. Moreover, sensitivity analyses were performed in different subgroups to further assess the role of several of the more important potential confounders. Fourth, logistic regression modeling was performed according to recommended guidelines, including using an appropriately large sample size (5 to 10 outcomes for each independent variable) and ensuring that the continuous independent variables were classified in such a manner as to conform to the linearity assumption of logistic regression.²² As a demonstration of the importance of the latter, when the nonlinear relationship of nHct with ARF-D was ignored and it was analyzed as a simple continuous variable, it was no longer independently associated with ARF-D (results not shown). Finally, this study included the entire cardiac surgery case-mix of a single tertiary referral center in which patient management was standardized. This increases the generalizability of the results and at the same time ensures that the observed association is not due to variations in clinical practice.

Study Limitations

The results of our study must be interpreted cautiously for several reasons. First, the database was created before this study was conceived. Second, because it was an observational study, interpretation of the results should be limited to associations between variables of interest; no causal inferences should be drawn. Third, and most important, the influence of unmeasured but potentially confounding variables on the observed association cannot be entirely ruled out. For example, we did not collect, and therefore could not control for, patients' fluid balance. It is possible (but, given

the standardized practice of CPB and fluid management at this institution, improbable) that patients with lower nHct were overhydrated and that those with higher nHct were underhydrated. Such a systematic difference in hydration status would confound the observed relationship between hemodilution during CPB and ARF-D. Other possible confounders include systematic differences in the type and the dose of colloids and antifibrinolytics, both of which may affect perioperative hemodilution and postoperative renal function. Fourth, given that the observed association between mild and moderate hemodilution was not significant in the subgroup analysis, it cannot be concluded that the risk of ARF-D is higher with mild versus moderate hemodilution. Larger studies are required to provide a more accurate estimate of this relationship.

Clinical Implications

Thus, despite the strengths of this study, we cannot recommend that the practice of CPB be modified to maintain patients' hematocrit concentration within the "optimal" range identified in this study. Before one can make such a recommendation, which would entail increasing the currently accepted transfusion trigger during CPB, this finding must first be confirmed by randomized controlled trials that compare the renal effects of different hematocrit concentrations during CPB. This is particularly important given that some of the available options for maintaining higher hematocrit concentrations during CPB are not risk free. For example, increasing the transfusion trigger during CPB may reduce the risk of ARF, but it will concomitantly expose patients to all the attendant risks of blood transfusion. Other options, such as retrograde priming of the CPB circuit with autologous blood, reducing the prime volume by using smaller circuits, and ultrafiltration during CPB, may not be appropriate in every case and may increase costs.

On the basis of the results of this study, as well as those of other studies that have found an association between the degree of hemodilution during CPB and postoperative organ dysfunction and mortality, it is our conclusion that random-

ized controlled trials comparing different degrees of hemodilution are now mandated to determine whether there is an "optimal" degree of hemodilution during CPB.

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