Risk Associated With Preoperative Anemia in Cardiac Surgery

A Multicenter Cohort Study

Keyvan Karkouti, MD; Duminda N. Wijeysundera, MD; W. Scott Beattie, MD; for the Reducing Bleeding in Cardiac Surgery (RBC) Investigators

Background—Preoperative anemia is an important risk factor for perioperative red blood cell transfusions, which are associated with postoperative morbidity and mortality. Whether preoperative anemia also is an independent risk factor for adverse outcomes after cardiac surgery, however, has not been fully elucidated.

Methods and Results—In this multicenter cohort study, data were collected on 3500 consecutive patients who underwent cardiac surgery during 2004 at 7 academic hospitals. The prevalence of preoperative anemia, defined as hemoglobin <12.5 g/dL, and its unadjusted and adjusted relationships with the composite outcome of in-hospital death, stroke, or acute kidney injury were obtained. The overall prevalence of preoperative anemia was 26%, with values ranging from 22% to 30% at the participating hospitals. After the exclusion of patients who had severe preoperative anemia (hemoglobin <9.5 g/dL) or preoperative kidney failure and those who underwent emergency surgery, the composite outcome was observed in 7.5% of patients (247 of 3286). The unadjusted odds ratio for the composite outcome in anemic versus nonanemic patients was 3.6 (95% confidence interval, 2.7 to 4.7). The risk-adjusted odds ratios, obtained by multivariable logistic regression and propensity-score matching to control for important confounders (including comorbidities, institution, surgical factors, and blood transfusion), were 2.0 (95% confidence interval, 1.4 to 2.8) and 1.8 (95% confidence interval, 1.2 to 2.7), respectively.

Conclusions—Preoperative anemia is independently associated with adverse outcomes after cardiac surgery. Future studies should determine whether therapies aimed at treating preoperative anemia would improve the outcomes of patients undergoing cardiac surgery. **(*Circulation*. 2008;117:478-484.)**

Key Words: anemia ■ risk factors ■ surgery

Preoperative anemia in cardiac surgery is an important health issue. Cardiac surgery is common, with ≈646 000 open-heart operations performed annually in the United States alone,[1] and it consumes a substantial portion (up to 20%) of the red blood cell (RBC) supply.[2] Preoperative anemia is important because it is the single most important determinant of perioperative RBC transfusions,[3] which have many risks and side effects.[4,5] Preoperative anemia also may have independent harmful effects, as suggested by recent data in the general and elderly populations,[6,7] in patients with coronary artery disease and congestive heart failure,[8–10] and in cardiac surgery,[11–13] in which anemia has been shown to be an independent risk factor for short- and long-term morbidity and mortality.

Clinical Perspective p 484

Preoperative anemia, if found to be an important cause of (rather than simply being associated with) adverse outcomes after cardiac surgery, is also a convenient target for intervention. The 3 most common causes of preoperative anemia in cardiac surgery are hospital-acquired anemia, iron-deficiency anemia, and anemia of chronic disease,[14] all of which are readily diagnosable and treatable. Despite the heavy burden of preoperative anemia in cardiac surgery and the ease with which it can be diagnosed and treated, only 3 studies have examined in depth the implications of preoperative anemia in cardiac surgery.[15–17] These studies, however, were for the most part limited by small sample size, single-center design, or the failure to account for important confounders. In view of these limitations, we undertook a multicenter, retrospective cohort study to delineate the independent relationship between preoperative anemia and outcomes after cardiac surgery.

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

Received May 29, 2007; accepted November 20, 2007.

From the Departments of Anesthesia (K.K., D.N.W., W.S.B.) and Health Policy, Management, and Evaluation (K.K., D.N.W.), University Health Network, University of Toronto, Toronto, Ontario, Canada.

The online Data Supplement, which contains a list of the RBC investigators, can be found with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.718353/DC1.

Correspondence to Keyvan Karkouti, MD, University Health Network, Toronto General Hospital, Department of Anesthesia, EN 3–402, 200 Elizabeth St, Toronto, Ontario, Canada, M5G 2C4. E-mail keyvan.karkouti@uhn.on.ca

Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.107.718353

Methods

Study Setting, Patient Sample, and Data Collection

Seven university-affiliated Canadian hospitals participated in the study. After institutional research ethics board approval was obtained, data were retrospectively collected on 500 consecutive adult (>18 years of age) patients who underwent cardiac surgery with cardiopulmonary bypass (CPB) at each hospital in 2004. Patients were identified from hospital administrative databases in reverse chronological order starting from December 31, 2004. If a patient underwent >1 relevant procedure during the study period, only the initial surgery was included for analysis. We excluded cases involving heart transplantation, ventricular assist device placement, or repair of complex congenital abnormalities because these procedures were not performed at all participating hospitals.

Using standardized case report forms, we collected detailed perioperative data (including demographics, laboratory tests, nature of surgery, blood product transfusions, re-exploration rates, postoperative complications, and lengths of stay in the intensive care unit and hospital) from existing clinical databases and hospital charts. Data were entered into a computerized database, which was programmed to accept only matching double-entry data falling within prespecified ranges. All queries were resolved by referring to the patients' original records.

Dependent Variable

The primary dependent variable was the composite outcome of in-hospital death, stroke (any persistent new neurological deficit after surgery), or acute kidney injury (>2-fold increase in creatinine concentration to above normal levels of 100 μmol/L in women and 110 μmol/L in men or the need for dialysis support).

Statistical Analyses

SAS version 9.1 (SAS Institute, Inc, Cary, NC) and R 2.3.1 (R Foundation for Statistical Computing, Vienna, Austria) were used for the statistical analyses. Categorical variables were summarized as frequencies and percentages; continuous variables were summarized as means and SDs. Patients who had severe anemia (hemoglobin <9.5 g/dL), required emergency surgery, or were dialysis dependent were excluded from analyses because anemia in these patients is most likely to be a marker for severity of illness.

The prevalence of preoperative anemia, defined as a hemoglobin concentration <12.5 g/dL (which is the average threshold of the World Health Organization's gender-based definition of 12.0 g/dL in women and 13.0 g/dL in men),[18] was measured at each of the hospitals. We also graphically evaluated the unadjusted association between preoperative hemoglobin and composite adverse outcome. Specifically, we calculated the prevalence of the composite adverse event within classes defined by preoperative hemoglobin (categorized in 1.5-g/dL increments from 9.5 to ≥15.5 g/dL).

Multivariable logistic regression modeling was carried out to assess the independent relationship between preoperative anemia and the composite adverse outcome. Initially, bivariate analyses (using the χ^2 statistic for categorical variables and the *t* test or Wilcoxon rank-sum test for continuous variables) were carried out to identify preoperative and intraoperative variables that were associated with preoperative anemia, as defined above, and the composite adverse outcome. The mathematical relationships between the continuous independent variables and the composite outcome were assessed through the use of cubic spline functions.[19,20] Variables that were not linearly related were mathematically transformed, categorized along appropriate cut points, or converted into multiple dichotomous variables.[21] All clinically sensible variables with values of $P<0.3$ in bivariate associations were entered into a multivariable logistic regression model. Subsequent retention in this model was determined with backward stepwise selection, where $P<0.1$ was the criterion for variable retention. A Pearson correlation matrix of variables was used to identify collinear independent variables.[21]

In sensitivity analyses, 2 additional models were constructed that excluded patients on the basis of whether they had received RBC transfusions intraoperatively or had undergone nonelective surgery.

We assessed model discrimination using the c index and calibration using the Hosmer-Lemeshow statistic (larger probability value means better calibration) and an observed-versus-predicted plot. To correct for possible overoptimism in these estimates, we also used bootstrap methods (n=200) to calculate bias-corrected estimates of discrimination and calibration.[22,23]

Propensity Score–Based Matching

Patient matching based on propensity scores was used to obtain an approximately unbiased estimate of the effects of preoperative anemia on the composite outcome by balancing measured covariates in anemic and nonanemic patients.[24] The propensity score for preoperative anemia was derived with a multivariable logistic regression model. The regression model included all measured independent variables that could be related to preoperative anemia, as well as important 2-way interaction terms.

Using a 5→1 computerized greedy matching technique, patients with preoperative anemia were then matched 1:1 to patients without preoperative anemia on the basis of similar propensity scores.[25] Measured covariates and adverse postoperative events in these matched pairs were compared by use of a paired *t* test or Wilcoxon signed-rank test for continuous variables and conditional matched-pair logistic regression for categorical variables.[26,27]

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

The study included 3500 patients; each hospital contributed 500 patients. Sixty-seven percent of patients underwent isolated coronary artery bypass graft surgery, 9% underwent single-valve procedures (repair or replacement), and 24% underwent other types of procedures, primarily combined coronary artery bypass graft surgery and valve surgery or aortic surgery. Ten patients with missing preoperative hemoglobin values were excluded from analysis. Sixty-two patients who were missing ≥1 confounding variables were excluded from the multivariable analyses (logistic regression and propensity score matching).

The mean (±SD) preoperative hemoglobin concentration was 13.4±1.7 g/dL, with values ranging from 5.8 to 18.0 g/dL. The overall prevalence of anemia, defined as hemoglobin concentration <12.5 g/dL, was 26%, with values ranging from 22% to 30% at the participating hospitals.

Figures 1 and 2 show the unadjusted relationships (using histograms and spline functions, respectively) between preoperative hemoglobin concentration and the composite outcome after patients who had severe anemia (hemoglobin <9.5 g/dL), required emergency surgery, or were dialysis dependent preoperatively were excluded (total excluded, 204). The unadjusted relationships of preoperative anemia with perioperative variables and measured outcomes in the 3286 patients retained in the analyses are shown in Tables 1 and 2, respectively. The unadjusted odds of the composite outcome was 360% higher in anemic than nonanemic patients (odds ratio [OR], 3.6; 95% confidence interval [CI], 2.7 to 4.7; $P<0.0001$) (Table 3).

Adjusting for Confounders by Multivariable Logistic Regression Modeling

In the logistic regression models assessing the relationship between preoperative anemia and the adverse composite outcome, intraoperative RBC transfusions were included as a confounding variable, categorized as 0, 1 to 2, 3 to 4, 4 to 6, and

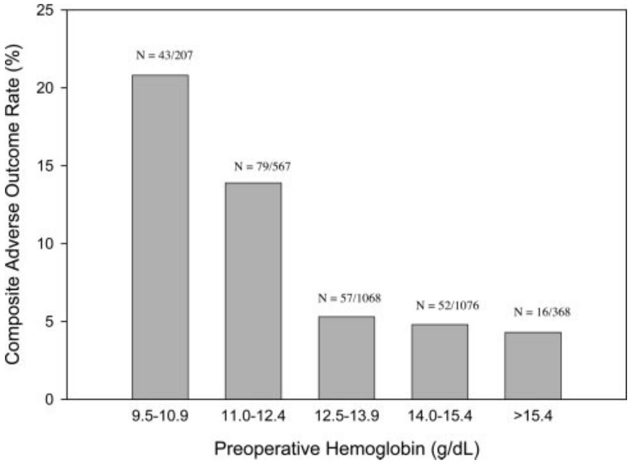

Figure 1. Unadjusted association between preoperative hemoglobin concentration and the composite adverse outcome. Vertical bars represent proportions with the composite adverse outcome within categories defined by preoperative hemoglobin.

≥7 U. Other confounding variables assessed were the following patient variables: sex, age, weight, hypertension, diabetes, chronic obstructive pulmonary disease, peripheral vascular disease, cerebrovascular disease, atrial fibrillation, left ventricular ejection fraction, recent myocardial infarction, recent cardiac catheterization, renal function, medications (acetylsalicylic acid, clopidogrel), and coagulation status (platelet count, international normalized ratio of prothrombin time, partial thromboplastin time), as well as the following surgical variables: hospital, surgeon (categorized into 2 groups based on whether their composite adverse outcome rate was greater or less than the median rate in the entire sample), urgency, procedure type, previous sternotomy, CPB duration, deep hypothermic circulatory arrest, type of antifibrinolytic drug used, lowest hematocrit during CPB, and hemoglobin concentration at admission to the intensive care unit. No 2 variables had a Pearson correlation coefficient >0.4, thereby suggesting that collinearity was not a concern in the logistic regression analyses.

After these variables were controlled for, preoperative anemia was independently associated with the composite adverse outcome (OR, 2.0; 95% CI, 1.4 to 2.8; $P<0.0001$) (Table 3). The model had good calibration (Hosmer-Lemeshow test, $P=0.3$) and discrimination (c index, 0.82; bias corrected, 0.79). Preoperative anemia was the second most predictive variable in the model; CPB duration was the most predictive variable. Other predictive variables, in order of importance, were surgeon, RBC transfusion, age, weight, preoperative atrial fibrillation, diabetes, procedure type, hypertension, recent myocardial infarction, preoperative left ventricular dysfunction, preoperative thrombocytopenia, urgency of procedure, and preoperative renal dysfunction. Addition of interaction terms did not significantly influence the model. The models were similar when patients were included on the basis of whether they had received intraoperative RBC transfusions (Table 3) or had undergone nonelective surgery (not shown).

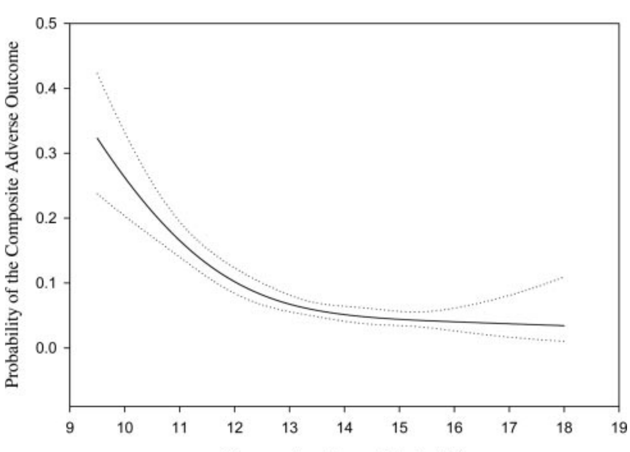

Figure 2. Spline function graph of the unadjusted relationship between preoperative hemoglobin concentration and probability of the composite adverse outcome. Top and bottom lines represent the 95% CI of the relationship.

Adjusting for Confounders by Propensity Score Matching

The propensity score was based on a nonparsimonious logistic regression model with 28 included variables. The score performed well in balancing measured confounders. Before matching, there were 29 statistically significant differences between anemic and nonanemic patients with regard to perioperative characteristics (Table 1). In the course of propensity-score matching, we successfully matched 515 anemic patients to 515 nonanemic patients. Other than preoperative hemoglobin concentration, the matched pairs did not differ with regard to any perioperative characteristics (Table 1). Importantly, the matched pairs had similar intraoperative RBC transfusion rates (Table 1), which suggests that blood loss was greater in the matched nonanemic patients. Consistent with this, platelet and plasma transfusion rates were higher in the nonanemic patients compared with their matched anemic counterparts (Table 1). Despite having balanced confounders and possibly lower blood loss, matched anemic patients had higher adverse outcomes rates than their nonanemic counterparts (Table 2). The odds ratio of the composite adverse outcome in the matched anemic patients was 1.8 (95% CI, 1.2 to 2.7) (Table 3).

Discussion

In this retrospective study of consecutive patients who underwent cardiac surgery at 7 hospitals during 2004, we found that preoperative anemia was a highly prevalent condition that was independently associated with adverse outcomes. In this sample, fully one quarter of patients were anemic (hemoglobin <12.5 g/dL) on presentation for nonemergency surgery. Moreover, after adjustment for important preoperative and perioperative confounders, anemic patients had a markedly greater odds of suffering an adverse outcome (death, stroke, or acute kidney injury) than nonanemic patients.

To date, the prognostic value of anemia has been studied primarily in nonoperative settings, where it has been shown to be an important risk factor for short- and long-term outcomes in the general and elderly populations,[6,7] patients with coronary artery disease,[8,9] and patients with congestive heart failure.[10] Several studies also have found preoperative anemia to be predictive of adverse outcomes in cardiac surgery.[11–13] Consistent with these studies, our study indicates that preoperative anemia is an important risk factor for short-term complications in patients undergoing cardiac surgery. Moreover, because the risks of

Table 1. Patient Demographics and Perioperative Variables At Participating Hospitals

	Entire Sample			Propensity-Matched Group		
Variables	Nonanemic (n=2512)	Anemic (n=774)	*P*	Nonanemic (n=515)	Anemic (n=515)	*P*
Patient demographics and comorbidities						
Female sex, n (%)	443 (18)	361 (47)	<0.0001	195 (38)	206 (40)	0.5
Age, y	64±11	69±11	<0.0001	68±10	67±11	0.5
Weight, kg	83±17	76±16	<0.0001	78±16	77±16	0.3
Diabetes mellitus (type I or II), n (%)	670 (27)	312 (40)	<0.0001	184 (36)	189 (37)	0.7
Hypertension, n (%)	1649 (66)	547 (71)	0.009	361 (70)	346 (67)	0.3
COPD, n (%)	233 (9)	99 (13)	0.005	64 (12)	63 (12)	0.9
Cerebrovascular disease, n (%)	206 (8)	116 (15)	<0.0001	72 (14)	63 (12)	0.4
Peripheral vascular disease, n (%)	237 (9)	131 (17)	<0.0001	69 (13)	70 (14)	0.9
Atrial fibrillation, n (%)	206 (8)	103 (13)	<0.0001	56 (11)	61 (12)	0.6
Recent myocardial infarction, n (%)	372 (15)	197 (25)	<0.0001	110 (21)	98 (19)	0.4
Recent heart catheterization, n (%)	530 (21)	201 (26)	0.004	124 (24)	117 (23)	0.6
Left ventricular ejection fraction ≤40%, n (%)	357 (14)	151 (20)	0.0004	89 (17)	90 (17)	0.9
Renal dysfunction (creatinine >100 μmol/L in women, >110 μmol/L in men), n (%)	377 (15)	269 (35)	<0.0001	135 (26)	131 (25)	0.8
Thrombocytopenia (platelet $<150\times10^9$/L), n (%)	160 (6)	70 (9)	0.01	39 (8)	40 (8)	0.9
Coagulopathy (INR >1.5), n (%)	70 (3)	38 (5)	0.004	20 (4)	26 (5)	0.4
Preoperative medications, n (%)						
Heparin (within 24 h of surgery)	323 (13)	185 (24)	<0.0001	98 (19)	96 (19)	0.9
Acetylsalicylic acid (within 5 d of surgery)	1169 (46)	326 (42)	0.03	239 (46)	221 (43)	0.3
Clopidogrel (within 5 d of surgery)	212 (8)	102 (13)	<0.0001	66 (13)	57 (11)	0.4
Angiotensin-converting enzyme inhibitor	1468 (58)	450 (58)	0.9	319 (62)	301 (58)	0.3
Surgical variables						
Hospital, n (%)			0.04			0.9
1	358 (14)	121 (16)		86 (17)	79 (15)	
2	351 (14)	104 (13)		58 (11)	66 (13)	
3	342 (14)	124 (16)		84 (16)	80 (16)	
4	381 (15)	92 (12)		70 (14)	68 (13)	
5	358 (14)	105 (14)		74 (14)	66 (13)	
6	348 (14)	129 (17)		74 (14)	84 (16)	
7	374 (15)	99 (13)		69 (13)	72 (14)	
Cases operated on by surgeons whose composite complication rate was greater than the median rate in the entire sample, n (%)	1204 (48)	445 (57)	<0.0001	274 (53)	274 (53)	1.0
Procedures other than isolated coronary artery bypass grafting or single-valve repair/replacement, n (%)	544 (22)	217 (28)	0.0002	133 (26)	136 (26)	0.8
Urgent surgery, n (%)	310 (12)	122 (16)	0.01	90 (17)	77 (15)	0.3
Redo surgery, n (%)	175 (7)	74 (10)	0.02	54 (10)	46 (9)	0.4
CPB duration	107±47	113±54	0.003	110±50	113±54	0.3
Deep hypothermic circulatory arrest, n (%)	62 (2)	17 (2)	0.7	11 (2)	12 (2)	0.8
Aprotinin used, n (%)	659 (26)	242 (31)	0.006	148 (29)	163 (32)	0.3
Re-exploration, n (%)	134 (5)	64 (8)	0.003	34 (7)	35 (7)	0.9
Postoperative duration of hospitalization, d	8±10	11±22	<0.0001	11±13	11±14	0.6
Perioperative Hb/Hct variables						
Hb, preoperative, g/dL*	14.2±1.1	11.3±0.8	<0.0001	13.7±0.9	11.5±0.7	<0.0001
Hct, lowest during CPB, %	25±3	21±3	<0.0001	22±3	22±2	0.8
Hb, ICU admission, g/dL	9.5±1.7	8.8±1.8	<0.0001	8.8±2.0	8.9±1.5	0.3

(*Continued*)

Table 1. Continued

Variables	Entire Sample Nonanemic (n=2512)	Entire Sample Anemic (n=774)	Entire Sample *P*	Propensity-Matched Group Nonanemic (n=515)	Propensity-Matched Group Anemic (n=515)	Propensity-Matched Group *P*
Transfusion variables, n (%)						
Intraoperative RBC transfusion, U			<0.0001			0.9
0	1939 (77)	255 (33)		224 (44)	230 (45)	
1–2	442 (18)	286 (37)		197 (38)	194 (38)	
3–4	94 (4)	173 (22)		70 (14)	68 (13)	
5–6	18 (1)	34 (4)		16 (3)	14 (3)	
>6	19 (1)	26 (3)		8 (2)	9 (2)	
≥1 U RBC transfusion in hospital*	1164 (46)	646 (83)	<0.0001	375 (73)	397 (77)	0.1
≥5 U RBC transfusion in hospital*	211 (8)	225 (29)	<0.0001	96 (19)	102 (20)	0.6
≥1 U platelet transfusion in hospital*	471 (19)	205 (26)	<0.0001	141 (27)	110 (21)	0.02
≥1 U plasma transfusion in hospital*	636 (25)	270 (35)	<0.0001	186 (36)	148 (29)	0.01

COPD indicates chronic obstructive pulmonary disorder; INR, international normalized ratio; Hb, hemoglobin; Hct, hematocrit; and ICU, intensive care unit. Unless otherwise specified, values are mean±SD.

*Variables that were not adjusted for in the multivariable analyses.

preoperative anemia were independent of RBC transfusions, our study highlights the particular importance of preoperative anemia as a risk factor in the cardiac surgery setting where it often necessitates RBC transfusions, exposing patients to the additional risks of RBC transfusions.[4,5]

To the best of our knowledge, the relationship between preoperative anemia and adverse outcomes in cardiac surgery has been examined in depth by only 3 previous studies, all of which found it to be independently associated with adverse postoperative outcomes.[15–17] In the study by Zindrou and associates,[15] in-hospital mortality of 62 severely anemic patients (hemoglobin ≤10.0 g/dL) was compared with that in 2075 nonanemic patients (hemoglobin >10.0 g/dL). After adjustment for several preoperative comorbidities, anemia was associated with approximately a 3-fold increase in the odds of in-hospital death (OR, 3.2; 95% CI, 1.2 to 8.1). In the study by Cladellas and associates,[16] in-hospital morbidity and mortality of 42 anemic patients (hemoglobin <12.0 g/dL) were compared with those of 159 nonanemic patients (hemoglobin ≥12.0 g/dL). After adjustment for several preoperative comorbidities, anemia was associated with a >3-fold increase in the odds of death (OR, 3.2; 95% CI, 1.1 to 9.55) and a >5-fold increase in the odds of major complications (OR, 5.2; 95% CI, 2.2 to 1.44). In the study by Kulier and associates,[17] the relationship between preoperative anemia with cardiac and noncardiac adverse events was assessed in 4804 patients who underwent cardiac surgery at 72 institutions during the 1990s, with multivariable logistic regression used to adjust for the effects of confounders. This study found a strong independent association between preoperative anemia and noncardiac complications (which included cerebral, renal, gastrointestinal, and "other" adverse events) but not cardiac complications. After risk adjustment, each 1-g/dL drop in hemoglobin concentration below 14 g/dL was associated with an ≈15% increase in the odds of the composite noncardiac adverse events.[17]

Compared with previous studies, our study had several strengths. Most important, we adjusted for a greater number of confounders that included an extensive number of comorbidities, the institution where the surgery was performed, and the surgeon effect, as well as for important intraoperative variables such as CPB duration and intraoperative RBC transfusions. By adjusting for intraoperative RBC transfusions, we essentially compared patients who had preoperative anemia with those who did not have preoperative anemia but received similar amounts of intraoperative RBC transfusions. It would follow, therefore, that we compared anemic patients with nonanemic patients with greater perioperative blood loss, which would explain why plasma and platelet transfusion rates were substantially higher in the nonanemic patients. The fact that nonanemic patients had better outcomes than anemic patients, despite having lost more blood and having received more blood products perioperatively, attests to the robustness of our results and the importance of anemia as a risk factor for adverse outcomes.

Table 2. Measured Outcomes

In-Hospital Adverse Outcomes	Entire Sample Nonanemic (n=2512), n (%)	Entire Sample Anemic (n=774), n (%)	Entire Sample *P*	Propensity-Matched Group Nonanemic (n=515), n (%)	Propensity-Matched Group Anemic (n=515), n (%)	Propensity-Matched Group *P*
Death	36 (1.4)	51 (6.6)	<0.0001	16 (3.1)	24 (4.7)	0.2
Stroke	28 (1.1)	22 (2.8)	0.0006	9 (1.8)	15 (2.9)	0.2
Acute kidney injury (>100% increase in creatinine and above normal or dialysis)	91 (3.6)	82 (10.6)	<0.0001	26 (5.1)	49 (9.5)	0.006
Composite of death, stroke, or acute kidney injury	125 (5.0)	122 (15.8)	<0.0001	39 (7.6)	66 (12.8)	0.005

Table 3. Unadjusted and Adjusted Relationships Between Preoperative Anemia and the Composite Adverse Outcome

Analysis	Anemic/Total, n	Composite Outcome, n	Relationship Between Preoperative Anemia and Adverse Composite Outcome		Model Performance	
			OR (95% CI)	*P*	Hosmer-Lemeshow Test *P*	c Index
Unadjusted relationship, entire sample	774/3286	247	3.6 (2.7–4.7)	<0.0001	NA	0.64
Logistic regression, entire sample	758/3224	239	2.0 (1.4–2.8)	<0.0001	0.3	0.82
Logistic regression, including only patients who received intraoperative RBC transfusions	509/1079	143	2.0 (1.3–3.1)	0.001	0.5	0.76
Logistic regression, excluding patients who received intraoperative RBC transfusions	249/2145	96	2.3 (1.3–4.1)	0.003	0.5	0.85
Propensity-matched sample	515/1030	105	1.8 (1.2–2.7)	0.005	0.2	0.87

Other strengths of our study were that it included a large number of consecutive patients who underwent a wide variety of cardiac surgical procedures at multiple hospitals in the recent past and that it used a comprehensive, accurate set of data obtained by data abstractors who were blinded to the objectives of this study. Moreover, our results were consistent using 2 different statistical risk adjustment methods, namely multivariable logistic regression and propensity-score matching. Finally, we used explicit outcomes that are easily diagnosable after cardiac surgery. These characteristics enhance the generalizability and validity of our results.

There are several limitations to be considered when our study is interpreted. First, because this was a retrospective observational study, causality could not be determined. Therefore, it is possible that preoperative anemia was associated with adverse outcomes simply because it is a marker for severity of illness. Second, the effects of unknown or unmeasured confounders on the observed association cannot be ruled out. Owing to the breadth of the variables we included in our multivariable analyses and the robustness of our results, however, the effects of any such confounders are unlikely to be large. Third, neither the cause nor the duration of preoperative anemia, both of which have prognostic implications, was known. Excluding those most likely to have acute anemia (nonelective cases), however, did not have a material effect on our results (not shown). Fourth, the duration of follow-up was limited to the period of hospitalization. Thus, postdischarge complications could not be accounted for in our analysis.

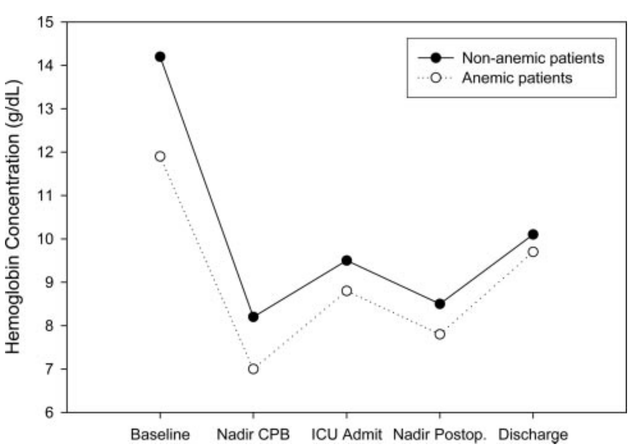

Figure 3. Perioperative hemoglobin concentrations among non-anemic (baseline hemoglobin ≥12.5 g/dL) and anemic (baseline hemoglobin <12.5 g/dL) patients. *P*<0.0001 at all time points. ICU indicates intensive care unit.

Another limitation of our study is that we could not delineate the mechanisms by which preoperative anemia may lead to adverse outcomes. We did find, however, that hemoglobin concentrations throughout the perioperative period were markedly lower in patients with preoperative anemia than in those without preoperative anemia (Figure 3), even though perioperative RBC transfusion triggers were not dependent on patients' preoperative hemoglobin status. This suggests that patients with preoperative anemia may be at risk for inadequate tissue oxygen delivery at some points during the perioperative period, resulting in impaired tissue oxygenation and organ dysfunction. Consistent with this hypothesis, there is experimental evidence that oxygen supply to critical organs is compromised during the early stages of anemia.[28] Moreover, several recent clinical studies have found that severe anemia and low oxygen delivery during CPB are associated with increased risk of renal failure, stroke, and death.[29–33]

The findings of this study may have important clinical implications. If the observed association between preoperative anemia and adverse outcomes in cardiac surgery is indeed causal, then diagnosing and correcting preoperative anemia may improve outcomes. Because available therapies (iron and erythropoietin) are not risk free and may necessitate delay of surgery, however, randomized controlled clinical trials are warranted to determine whether treating preoperative anemia improves outcomes in cardiac surgical patients.

Conclusions

This multicenter retrospective study found that preoperative anemia was independently associated with adverse outcomes after cardiac surgery. Importantly, this association was independent of the effects of RBC transfusion. Future studies should determine whether therapies aimed at treating preoperative anemia would improve perioperative outcomes of patients undergoing cardiac surgery.

Source of Funding

The Canadian Institutes of Health Research provided funding for this project.

Disclosures

None.

References

1. Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenlund K, Haase N, Ho M, Howard V, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell CJ, Roger V, Rumsfeld J, Sorlie P, Steinberger J, Thom T, Wasserthiel-Smoller S, Hong Y. Heart disease and stroke statistics: 2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2007;115:e69–e171.
2. Van der LP, Dierick A. Blood conservation strategies in cardiac surgery. *Vox Sang*. 2007;92:103–112.
3. Khanna MP, Hebert PC, Fergusson DA. Review of the clinical practice literature on patient characteristics associated with perioperative allogeneic red blood cell transfusion. *Transfus Med Rev*. 2003;17:110–119.
4. Vincent JL, Baron JF, Reinhart K, Gattinoni L, Thijs L, Webb A, Meier-Hellmann A, Nollet G, Peres-Bota D. Anemia and blood transfusion in critically ill patients. *JAMA*. 2002;288:1499–1507.
5. Spiess BD. Transfusion of blood products affects outcome in cardiac surgery. *Semin Cardiothorac Vasc Anesth*. 2004;8:267–281.
6. Sarnak MJ, Tighiouart H, Manjunath G, MacLeod B, Griffith J, Salem D, Levey AS. Anemia as a risk factor for cardiovascular disease in the Atherosclerosis Risk in Communities (ARIC) study. *J Am Coll Cardiol*. 2002;40:27–33.
7. Izaks GJ, Westendorp RG, Knook DL. The definition of anemia in older persons. *JAMA*. 1999;281:1714–1717.
8. Sabatine MS, Morrow DA, Giugliano RP, Burton PB, Murphy SA, McCabe CH, Gibson CM, Braunwald E. Association of hemoglobin levels with clinical outcomes in acute coronary syndromes. *Circulation*. 2005;111:2042–2049.
9. Reinecke H, Trey T, Wellmann J, Heidrich J, Fobker M, Wichter T, Walter M, Breithardt G, Schaefer RM. Haemoglobin-related mortality in patients undergoing percutaneous coronary interventions. *Eur Heart J*. 2003;24:2142–2150.
10. Tang YD, Katz SD. Anemia in chronic heart failure: prevalence, etiology, clinical correlates, and treatment options. *Circulation*. 2006;113:2454–2461.
11. Magovern JA, Sakert T, Magovern GJ, Benckart DH, Burkholder JA, Liebler GA, Magovern JG. A model that predicts morbidity and mortality after coronary artery bypass graft surgery. *J Am Coll Cardiol.* 1996;28:1147–1153.
12. Higgins TL, Estafanous FG, Loop FD, Beck GJ, Blum JM, Paranandi L. Stratification of morbidity and mortality outcome by preoperative risk factors in coronary artery bypass patients: a clinical severity score. *JAMA*. 1992;267:2344–2348.
13. Nilsson J, Ohlsson M, Thulin L, Hoglund P, Nashef SA, Brandt J. Risk factor identification and mortality prediction in cardiac surgery using artificial neural networks. *J Thorac Cardiovasc Surg*. 2006;132:12–19.
14. Karski JM, Mathieu M, Cheng D, Carroll J, Scott G. Etiology of preoperative anemia in patients undergoing scheduled cardiac surgery. *Can J Anaesth*. 1999;46:979–982.
15. Zindrou D, Taylor KM, Bagger JP. Preoperative haemoglobin concentration and mortality rate after coronary artery bypass surgery. *Lancet*. 2002;359:1747–1748.
16. Cladellas M, Bruguera J, Comin J, Vila J, de Jaime E, Marti J, Gomez M. Is pre-operative anaemia a risk marker for in-hospital mortality and morbidity after valve replacement? *Eur Heart J*. 2006;27:1093–1099.
17. Kulier A, Levin J, Moser R, Rumpold-Seitlinger G, Tudor IC, Snyder-Ramos SA, Moehnle P, Mangano DT. Impact of preoperative anemia on outcome in patients undergoing coronary artery bypass graft surgery. *Circulation*. 2007;116:471–479.
18. World Health Organization. Iron deficiency anaemia: assessment, prevention, and control: 2001. Available at: http://whqlibdoc.who.int/hq/2001/WHO_NHD_01.3.pdf. Accessed November 21, 2007.
19. Devlin TF, Weeks BJ. Spline functions for logistic regression modeling. *Proceedings of the 11th Annual SAS Users Group International Conference*. Cary, NC: SAS Institute Inc; 1986:646–651.
20. Harrell FE. SAS macros and data step programs useful in survival analysis and logistic regression: 1999. Available at: http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/SasMacros. Accessed November 21, 2007.
21. Katz MH. *Multivariable Analysis: A Practical Guide for Clinicians*. Cambridge, UK: Cambridge University Press; 1999.
22. Harrell FE. *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis*. New York, NY: Springer-Verlag; 2001.
23. Harrell FE. Design: S functions for biostatistical/epidemiologic modeling, testing, estimation, validation, graphics, and prediction: 2007. Available at: http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/Design. Accessed November 21, 2007.
24. D'Agostino RB. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med*. 1998;17:2265–2281.
25. Parsons LS. Reducing bias in a propensity score matched-pair sample using greedy matching techniques. *Proceedings of the 26th Annual SAS Users Group International Conference*. Cary, NC: SAS Institute Inc; 2004.
26. Schlesselman JJ. *Case-Control Studies: Design, Conduct, Analysis*. New York, NY: Oxford University Press; 1982.
27. Allison PD. Logit analysis of longitudinal and other clustered data. In: Allison PD, ed. *Logistic Regression Using SAS System: Theory and Application*. Cary, NC: SAS Institute and Wiley; 1991.
28. Johannes T, Mik EG, Nohe B, Unertl KE, Ince C. Acute decrease in renal microvascular Po_2 during acute normovolemic hemodilution. *Am J Physiol Renal Physiol*. 2007;292:F796–F803.
29. Ranucci M, Biagioli B, Scolletta S, Grillone G, Cazzaniga A, Cattabriga I, Isgro G, Giomarelli P. Lowest hematocrit on cardiopulmonary bypass impairs the outcome in coronary surgery: an Italian Multicenter Study from the National Cardioanesthesia Database. *Tex Heart Inst J*. 2006;33:300–305.
30. Ranucci M, Romitti F, Isgro G, Cotza M, Brozzi S, Boncilli A, Ditta A. Oxygen delivery during cardiopulmonary bypass and acute renal failure after coronary operations. *Ann Thorac Surg*. 2005;80:2213–2220.
31. 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;125:1438–1450.
32. 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.
33. 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;80:1381–1387.

CLINICAL PERSPECTIVE

In this multicenter cohort study of 3500 patients who underwent cardiac surgery with cardiopulmonary bypass, preoperative anemia (hemoglobin $<$12.5 g/dL) was found to be a strong, independent risk factor for adverse outcomes. After risk adjustment, anemic patients (n=774) had 2-fold (95% confidence interval, 1.4 to 2.8) greater odds for the composite adverse outcome of in-hospital death, stroke, or acute kidney injury than did nonanemic patients. If this is a causal relationship and preoperative anemia is not simply a marker for severity of illness, then diagnosing and correcting preoperative anemia may improve outcomes. Because available therapies (iron and erythropoietin) are not risk free and may necessitate delay of surgery, however, randomized controlled clinical trials are warranted to determine whether treating preoperative anemia improves outcomes in patients undergoing cardiac surgery.

Go to http://cme.ahajournals.org to take the CME quiz for this article.