The Association Between Duration of Storage of Transfused Red Blood Cells and Morbidity and Mortality After Reoperative Cardiac Surgery

Sukhjeewan Basran, MD

Robert J. Frumento, MS, MPH

Allison Cohen, BS

Samuel Lee, MD

Yuling Du, PhD

Ervant Nishanian, MD, PhD

Harold S. Kaplan, MD

Mark Stafford-Smith, FRCPC

Elliott Bennett-Guerrero, MD

Red blood cells (RBCs) undergo numerous changes during storage; however, the clinical relevance of these storage "lesions" is unclear. We hypothesized that the duration of storage of transfused RBCs is associated with mortality after repeat sternotomy for cardiac surgery, because these patients are at high risk for both RBC transfusion and adverse outcome. We retrospectively analyzed 434 patients who underwent repeat median sternotomy for coronary artery bypass graft or valve surgery and who received allogeneic RBCs. Three-hundred-twenty-one (74%) patients met the criteria for eligibility. After adjusting for the effects of confounders and the total number of RBC transfusions, the duration of storage of the oldest RBC unit transfused was found to be associated with both in-hospital mortality (Cox proportional hazard ratio (HR) = 1.151; $P < 0.0001$) and out-of-hospital mortality (HR = 1.116; $P < 0.0001$). The mean duration of storage of transfused RBCs was also an independent predictor of in-hospital mortality (HR = 1.036; $P < 0.0001$). Independent associations between the duration of storage of transfused RBCs and acute renal dysfunction and intensive care unit and hospital length of stay were also observed. The duration of storage of RBCs is associated with adverse outcome after repeat sternotomy for cardiac surgery. The clinical significance of this finding should be investigated in a large, randomized, blinded clinical trial.

(Anesth Analg 2006;103:15–20)

More than 12 million units of allogeneic red blood cells (RBCs) are administered in the United States annually, with more than 2 million units alone going to patients undergoing cardiovascular surgery (1). Patients undergoing repeat sternotomy for cardiac surgery are approximately three times more likely to receive a perioperative transfusion than those undergoing primary cardiac surgery (2). The transfusion of allogeneic RBCs has recently been described as a risk factor for decreased long-term survival after coronary artery bypass graft (CABG) surgery (3). RBC units are typically available for transfusion as early as 3–4 days after collection, and with modern preservation techniques, solutions can be administered up to 42 days after collection (4). As reviewed previously, the transfusion of stored RBCs may have adverse effects on critically ill patients (5). These adverse effects may be caused by storage-related changes, including the depletion of 2, 3 diphosphoglyceric acid and adenosine triphosphate, reduced RBC deformability (6,7), and a significant increase in abnormally shaped RBCs (8). These storage lesions might impair oxygen delivery to tissues by increasing capillary transit time and reducing oxygen unloading from hemoglobin (9). A study in trauma patients demonstrated that the mean duration of storage of RBCs, the number of RBC units stored for longer than 14 days, and the number of RBC units stored for more than 21 days were all independent risk factors for multiple-organ failure (MOF) (10). Additionally, two previous studies assessed the impact of duration of storage of RBCs in low-risk patients undergoing cardiac surgery (11,12). We speculated that the impact of duration of storage would be more pronounced in patients at high risk for multiple RBC transfusions and adverse outcome. Therefore, we tested the hypothesis that the duration of storage of transfused RBCs is associated with mortality and organ dysfunction after repeat sternotomy for cardiac surgery.

METHODS

This was a retrospective single-center study. Hospital IRB approval was obtained. A review of the hospital clinical perfusion database was performed to identify patients who underwent reoperative cardiac surgery between 1995 and March 2001. The medical record of each patient was then reviewed. Inclusion

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From the Departments of *Anesthesiology, †Internal Medicine, ‡Biostatistics, and §Clinical Perfusion, College of Physicians & Surgeons of Columbia University, New York; and ‖Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina.

Accepted for publication March 21, 2006.

Address correspondence and reprint requests to Elliott Bennett-Guerrero, MD, Department of Anesthesiology (Box 3094), Erwin Road, Duke University Medical Center, Durham, NC 27710. Address e-mail to Elliott.BennettGuerrero@Duke.edu.

DOI: 10.1213/01.ane.0000221167.58135.3d

criteria consisted of patients 18 years of age or older who underwent CABG or valve surgery under cardiopulmonary bypass (CPB) via a repeat median sternotomy. Patients were excluded if they underwent emergency surgery, surgery without CPB, cardiac transplantation, insertion of a mechanical assist device, received ≥1 U of irradiated allogenic RBCs, or required preoperative dialysis. Patients receiving irradiated blood were excluded because it was impossible for us to accurately determine the duration of storage of these RBCs.

From the hospital blood bank database, we recorded transfusions (allogeneic RBCs, platelet concentrate, and fresh frozen plasma [FFP]) administered during the surgical intervention and within the first 7 days after surgery. In almost all cases (>95%), the RBCs were stored in an AS type preservative, e.g., AS-1.

All demographic and outcome variables related to the study were collected by an investigator who was blinded to the duration of RBC storage.

In-hospital mortality was defined as any death occurring between the day of surgery and the day of discharge from the hospital regardless of cause. Out-of-hospital mortality was defined as any death occurring after discharge from the hospital through January 1, 2004. Mortality data for discharged patients were obtained from the United States Social Security Death Index database using patients name and their social security number as search criteria (ssdi.genealogy.rootsweb.com).

Given the retrospective nature of this study, we did not have accurate data related to postoperative organ dysfunction for most organ systems. However, serum creatinine was available in all patients and thus provided us with an opportunity to accurately assess this indicator of postoperative renal function. Consistent with previous studies (13,14), acute renal dysfunction (ARD) was defined as an increase in serum creatinine after surgery to ≥2 mg/dL with an increase of ≥0.7 mg/dL within 2 wk after surgery or the need for dialysis within 2 wk after surgery. This definition of ARD has been reported in more than 2800 cardiac surgical patients (13,14).

We also had accurate data for intensive care unit (ICU) length of stay (LOS) and hospital LOS, which are reasonable surrogates for the presence of organ dysfunction and recovery after surgery. ICU LOS was defined as the number of days from the day of operation (Day 0) to ICU discharge. Similarly, hospital LOS was defined as the number of days from the day of operation (Day 0) until discharge.

All patients received standard monitoring for cardiac surgery including electrocardiogram, transesophageal echocardiography, pulse oximetry, capnography, intraarterial catheterization for arterial blood pressure monitoring, and central venous and pulmonary artery catheterization. All patients received a balanced anesthetic regimen generally consisting of fentanyl, midazolam, 100% oxygen, and isoflurane. Surgical techniques and CPB included a standard centrifugal pump, nonpulsatile flow, hypothermia (32°C), and flow rates of $\geq 2.0\ \mathrm{L \cdot min^{-1} \cdot m^2}$.

Statistical calculation and analysis were performed using SPSS software (Berkeley, CA). The following variables were used to study the effect of RBC storage duration for each patient: (a) the mean duration of storage of all units of RBCs transfused and (b) the duration of storage of the oldest unit of RBCs transfused.

In our analyses, potential confounding variables included patient age, number of RBC units transfused (through postoperative Day 7), number of units of FFP transfused through 7 days after surgery, number of units of platelets transfused through 7 days after surgery, sex, New York Heart Association class, obesity (body mass index ≥30), diabetes mellitus (defined as the administration of oral glycemic drugs or insulin at the time of surgery), preoperative left ventricular ejection fraction, chronic obstructive pulmonary disease (defined as a clinical history of chronic bronchitis or emphysema), hypertension (defined as the administration of antihypertensive medications at the time of surgery), preoperative hematocrit, preoperative serum creatinine, surgical intervention (CABG, valve, or combination CABG-valve procedure), CPB duration, aortic cross-clamp duration, and the infusion of inotropic drugs on arrival to the ICU.

Cox proportional hazards (PH) method was used for the analyses of predictors for days to in-hospital death and days to out-of-hospital death. Initially, univariate analyses were conducted with the variables of primary interest, the durations of blood storage, and each covariate, including demographic variables and preoperative measurements. When any of the covariates were found to be marginally significant (P value <0.1) they were controlled for in tests of primary variables. Because the number of transfusions received could be viewed as a measure of severity of illness, correlations between the number of transfusions received and other predictors were assessed. After these analyses, a forward step-wise selection model was used to fit multivariate Cox PH models to investigate independent effects of predictors. To assess the validity of the PH assumption that the hazard ratio (HR) between two patients with different prognoses is constant over time, we created an artificial time-dependent variable for each predictor and tested the significance of the variable in the model. A significant finding indicates violation of the PH assumption. We further constructed figures to help us visually inspect the assumption. We divided the sample by quartiles of each predictor (except for sex, which is dichotomous), calculated the differences of log cumulative hazard functions between the first quartile subgroup and other quartile subgroups, and plotted the differences over time. If the assumption holds, the curves need to be roughly constant.

Table 1. Preoperative and Surgical Characteristics ($n = 321$)

Characteristic	
Age, yr	66.9 ± 10.4
Sex (% men)	224 (67.8%)
Preoperative hematocrit, %	37.2 ± 5.4
Preoperative creatinine, mg/dL	1.2 ± 0.9
CABG only	128 (39%)
Valve replacement/repair only	147 (46%)
Combined CABG/valve	48 (15%)
CPB duration, min	144 ± 58
AoX duration, min	89 ± 38

Values are mean ± SD or number (%).

CABG = coronary artery bypass graft; CPB = cardiopulmonary bypass; AoX = aortic cross-clamp.

Table 2. Multivariate Analysis of Predictors of In-Hospital Mortality Controlling for Patient Age, CPB Duration, and the Number of RBC Transfusions

Predictor	HR (95% CI)	*P*-value
Mean RBC storage duration	1.036 (1.02–2.98)	<0.0001
Maximum RBC storage duration	1.151 (1.04–2.01)	<0.0001
CPB duration	1.012 (1.00–3.12)	0.01
Occurrence of platelet transfusion	1.029 (1.02–2.06)	0.02
Preoperative serum creatinine	6.231 (1.62–14.98)	0.002

RBCs = red blood cells; CPB = cardiopulmonary bypass; HR = hazard ratio; CI = confidence interval; CABG = coronary artery bypass graft.

Initially, univariate analyses were conducted with each of the potential confounding variables. Variables related to duration of storage were then tested for entry into logistic regression models predicting the occurrence of postoperative renal dysfunction; these models included all corresponding confounders ($P < 0.1$) and were built by the forced-entry method while adjusting for the number of RBC transfusions administered. The Hosmer-Lemeshow test was used to evaluate the model's goodness-of-fit, which compares the number of observed and predicted cases of ARD in deciles of risk covering the entire range of probabilities of developing ARD.

The associations between hospital LOS and ICU LOS and the duration of storage of transfused RBCs were assessed by multiple linear regression analyses. Variables associated with (P value <0.1) both hospital LOS or ICU LOS and the duration of storage of transfused RBCs were identified as potential confounders and were entered into a multiple linear regression model. The duration of storage of transfused RBCs was tested for entry into these models after the inclusion of the identified confounding factors.

RESULTS

Of the 434 patients evaluated, 321 (74%) met the criteria for eligibility. Of note, 92 patients were excluded because they received ≥1 U of irradiated RBCs, which precluded the accurate determination of the duration of storage of these units. Of the 321 patients who were included in the analysis, 299 (93%) underwent first cardiac reoperation with a mean (±SD) of 7.4 yr (±2.9) from primary surgery. Preoperative and surgical characteristics are shown in Table 1. Two-hundred-one (63%) patients received platelet concentrates, and 151 patients (47%) received FFP. The mean (±SD) number of RBC units transfused was 5.2 (±4.2), ranged from 2 to 48 (median, 4.1), and 31 patients (10%) received ≥10 U over the 7-day period. Highlighting the importance of controlling in multivariate analyses for the total number of RBC units transfused, patients who received more RBC transfusions were more likely to receive a RBC unit of longer storage duration. Furthermore, there was a significant ($P < 0.001$) correlation between the number of units transfused and the maximum duration of storage of transfused RBC units per patient ($r = 0.346$), as well as the mean duration of storage of all RBC units transfused ($r = 0.209$).

Of the 321 patients studied, 26 (8%) died during their hospital stay. The mean (±SD) time to in-hospital death was 20.3 (±33.4) days. In univariate analyses, the mean duration of storage of transfused RBCs was a highly significant predictor of in-hospital mortality with a HR = 1.085 ($P < 0.000$). The HR value means that the hazard of in-hospital death is increased by 8.5% if the mean duration of blood storage is 1 day older. Other significant univariate predictors include the maximum duration of storage of transfused RBCs (HR = 1.080; $P = 0.0012$), the number of transfusions (HR = 1.079; $P < 0.001$), and the CPB duration (HR = 1.006; $P = 0.010$). The number of RBC transfusions received was significantly correlated with the mean duration of storage of transfused RBCs ($r = 0.209$; $P < 0.0001$), maximum duration of storage of transfused RBCs ($r = 0.348$; $P < 0.0001$), preoperative hematocrit ($r = -0.188$; $P = 0.001$), preoperative serum creatinine ($r = 0.199$; $P < 0.001$), and CPB duration ($r = 0.311$; $P < 0.001$). However, only preoperative creatinine ($P = 0.03$) and CPB duration ($P = 0.02$) showed an association with the maximum duration of storage of the oldest RBC unit transfused. After adjustment for the number of transfusions and CPB duration, both the maximum duration of storage of transfused RBCs and the mean duration of storage of transfused RBCs (Table 2) remained significant predictors of in-hospital mortality. For descriptive purposes, the rate of in-hospital mortality is presented by quartiles of maximum duration of storage of transfused RBCs (Fig. 1). In verification of the PH assumption, we did not detect that any of the variables violated the assumption.

Of the 295 patients who were discharged from the hospital, 46 (16%) died during the follow-up period. The duration of follow-up depended on the date of surgery and ranged from 32 to 96 mo. Significant univariate predictors of long-term mortality included

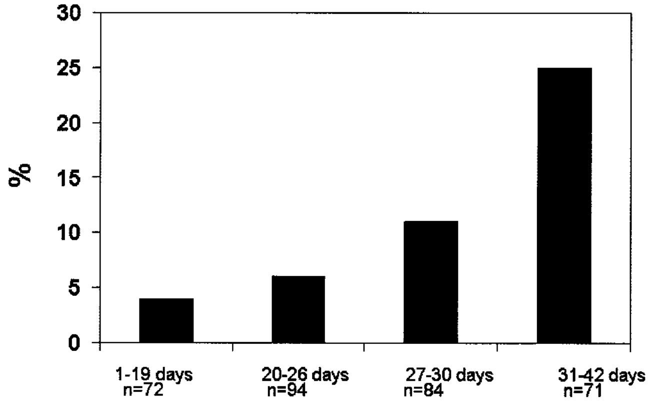

Figure 1. The rate of in-hospital mortality presented by quartiles of maximum duration of storage of transfused red blood cells (RBCs).

age (HR = 1.055; $P < 0.001$), mean RBC storage duration (HR = 1.102; $P < 0.001$), maximum RBC storage duration (HR = 1.116; $P < 0.001$), the total number of RBC transfusions (HR = 1.065; $P < 0.001$), CPB duration (HR = 1.003; $P = 0.037$), preoperative hematocrit (HR = 0.951; $P = 0.018$) and creatinine value (HR = 5.687; $P < 0.001$). The tests to verify the PH assumption revealed that age ($P = 0.000$) and preoperative hematocrit ($P = 0.045$) may violate the assumption, although the curves in both figures were relatively flat. Therefore, we only stratified on age grouped by quartiles in multivariate-adjusted analyses. When stratifying on age and adjusting for the total number of RBC transfusions both the mean duration of storage of transfused RBCs and the maximum duration of storage of transfused RBCs remained significant predictors of out-of-hospital mortality. Reported in Table 3 are results from the multivariate models with only significant predictors.

Of the 321 patients studied, 58 (18%) met published criteria (13) for ARD during their hospital stay. Univariate predictors of ARD were aortic cross-clamp duration (odds ratio [OR] = 1.001; $P = 0.04$), CPB duration (OR = 1.006; $P = 0.002$), preoperative serum creatinine (OR = 1.458; $P = 0.001$), patient age (OR = 1.020; $P = 0.09$), number of RBC transfusions (OR = 1.055; $P = 0.008$), mean RBC storage duration (OR = 1.219; $P < 0.001$), and maximum RBC storage duration (OR = 1.068; $P = 0.001$). The forced-entry method used to fit a multivariate logistic regression model predicting the development of ARD revealed that the total number of RBCs transfused was a significant predictor ($P = 0.009$) of postoperative ARD. After adjustment for the total number of RBC transfusions, the mean duration of storage of RBCs transfused was a significant independent predictor of ARD ($P = 0.025$). Similarly, the maximum storage duration of transfused RBCs was a significant independent predictor of postoperative ARD (Table 4). For descriptive purposes, the rate of ARD is presented by quartiles of maximum duration of storage of transfused RBCs (Fig. 2). The Hosmer-Lemeshow test used to evaluate the model's goodness-of-fit demonstrated a small value of the Hosmer-Lemeshow statistic (good calibration) and therefore indicates that the model provided an adequate estimation of the probability of ARD in these patients.

Table 3. Multivariate Analysis of Predictors of Out-of-Hospital Mortality Controlling for Patient Age and the Number of RBC Transfusions

Predictor	HR (95% CI)	*P*-value
Maximum RBC storage duration	1.116 (1.10–2.05)	<0.0001
CPB duration	1.053 (1.03–2.53)	0.01
Occurrence of platelet transfusion	1.078 (1.06–2.79)	0.02
Preoperative serum creatinine	5.687 (1.73–12.43)	0.002

RBCs = red blood cells; CPB = cardiopulmonary bypass; HR = hazard ratio; CI = confidence interval.

Table 4. Multivariate Analysis of Predictors of ARD Controlling for Patient Age and the Number of RBC Transfusions

Risk factor	OR	95% CI	*P*-value
Preoperative serum creatinine	2.584	1.6257–3.8835	0.001
Maximum RBC storage duration	1.445	1.0321–1.9476	0.01
Mean RBC storage duration	1.112	1.0879–1.2961	0.025

ARD = acute renal dysfunction; RBC = red blood cell; OR = odds ratio; CI = confidence interval.

There were overall associations between hospital ($P = 0.05$) and ICU ($P = 0.002$) LOS and the duration of storage of transfused RBCs. For descriptive purposes, hospital and ICU LOS are presented by quartiles of maximum duration of storage of transfused RBCs (Fig. 3). Significant univariates correlating to both hospital and ICU LOS included patients' age, duration of CPB, mean RBC storage duration, maximum RBC storage duration, the total number of RBC transfusions, CPB duration, preoperative hematocrit and creatinine value, and the occurrence of platelet

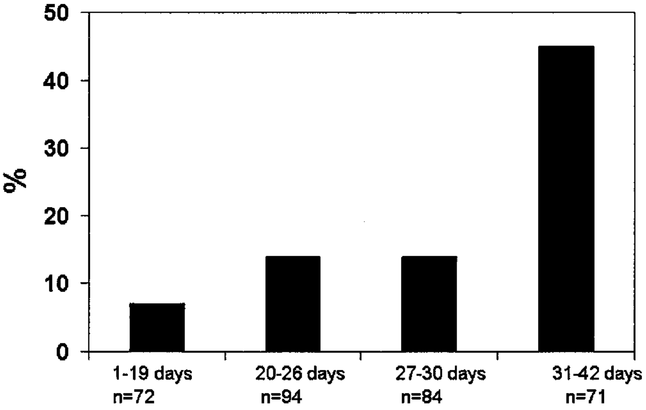

Figure 2. The rate of acute renal dysfunction (ARD) presented by quartiles of maximum duration of storage of transfused red blood cells (RBCs).

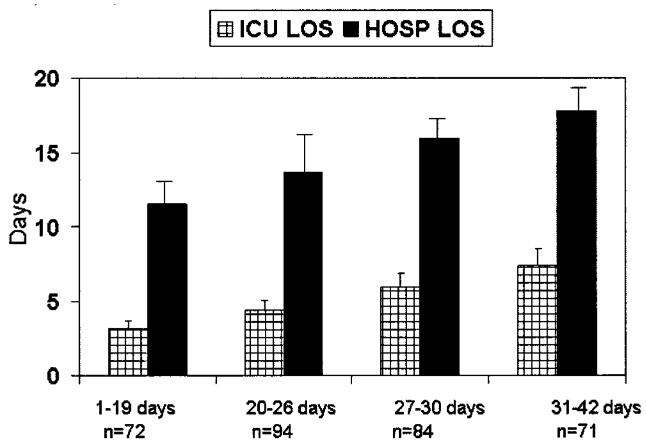

Figure 3. Intensive care unit (ICU) and hospital length of stay (LOS) presented by quartiles of maximum duration of storage of transfused red blood cells (RBCs).

transfusion. These variables were entered into a multivariate analysis predicting hospital and ICU LOS. In these analyses, only preoperative serum creatinine and the maximum duration of storage of transfused RBCs were significant predictors of either hospital or ICU LOS. The total number of RBC transfusions and the mean length of duration of all transfusions were no longer significant predictors in these analyses ($P = 0.53$ and $P = 0.89$, respectively).

DISCUSSION

The primary finding of this study is that the storage duration of perioperative transfused RBCs is associated with an increased risk of both short-term in-hospital and long-term out-of-hospital mortality independent of the number of transfusions administered and other confounding factors. Additionally, we observed an association between the duration of storage of perioperatively administered RBCs and the risk of postoperative ARD and an increase in ICU and hospital LOS after adjusting for the effects of confounding variables.

RBCs undergo significant changes during storage (7,8,15); however, the clinical relevance of these storage "lesions" is unclear. There are several studies in the critical care and trauma literature suggesting deleterious clinical effects associated with increased duration of storage of transfused RBCs. Purdy et al. (16) observed a correlation between the duration of storage of transfused RBCs and mortality in patients with severe sepsis independent of the number of transfusions received. Martin et al. (17) demonstrated that the duration of storage of transfused RBCs was associated with ICU LOS in anemic critically ill patients. In addition, Zallen et al. (10) demonstrated the average duration of storage of transfused RBCs was an independent risk factor for MOF in trauma patients. The relevance of these findings to patients undergoing cardiac surgery is unknown.

In contrast to our study, the only two other studies involving cardiac surgical patients did not assess the impact of duration of storage of RBCs on postoperative mortality. For example, Vamvakas and Carven (12,18) only included "low-risk patients unlikely to die during the hospitalization." Similarly, Leal-Noval et al. (11) excluded patients from their analysis of 795 cardiac surgical patients who died during the first few days after surgery. We hypothesized that any potential insult related to the duration of storage of transfused RBCs would be most evident in cardiac surgical patients who are at a higher risk of mortality and are more likely to receive multiple transfusions of RBCs. Therefore, we chose to study patients undergoing repeat sternotomy, because this surgery is associated with both an increased mortality rate (19) and an increased likelihood of multiple RBC transfusions (2). Indeed, 8% of our patients died in the hospital, and 16% died during the longer-term follow-up. In addition, the mean (±SD) number of RBC units transfused per patient was 5.2 (±4.2) and ranged from 2 to 48 (median, 4.1). This frequency of transfusion is consistent with previous studies (20,21).

It may be surprising that the duration of storage of transfused RBCs potentially affects long-term mortality, as we have shown. Interestingly, Engoren et al. (22) found an association between transfusion and five-year all-cause mortality in cardiac surgical patients, and Kuduvalli et al. (3) found an association between perioperative RBC transfusion and both 30-day and 1-year mortality after CABG. Their findings are compatible with ours and suggest that the transfusion of RBCs may have an impact on long-term survival after cardiac surgery. Furthermore, both Kuduvalli et al. (3) and Engoren et al. (22) observed an increased mortality rate in patients transfused both during and after surgery and hypothesized a dose-dependent relationship. We have also shown that the number of RBC transfusions given to each patient is a robust predictor of long-term mortality. Furthermore, we have shown that after controlling for the effects of the number of RBC transfusions received during the study period, the duration of storage of these transfusions has independent effects on long-term mortality.

We also explored the association of duration of storage with any outcomes that were readily available to us given the retrospective nature of this study. We were limited to analyzing organ dysfunction-recovery for variables that we had objective data for, e.g., serum creatinine and ICU and hospital LOS. Mangano et al. (13) reported an incidence of ARD after cardiac surgery of 8% when defined as a serum creatinine increase after surgery to ≥2 mg/dL with an increase of ≥0.7 mg/dL within two weeks after surgery or a need for dialysis within two weeks after surgery (13). Using identical criteria, we observed an incidence of 18%, which is not surprising because we enrolled higher-risk patients (reoperations) than those enrolled by Mangano et al (13). Indeed, several authors (13,23) have shown repeat sternotomy to be a significant risk factor for postoperative ARD. The association we have shown between the duration of storage of transfused RBCs and the risk of ARD may be linked to impaired RBC deformability that worsens during storage (8). Brown et al. (24) found that a progressive impairment in RBC deformability was significantly correlated with a loss of renal function in medical patients.

No large, randomized clinical trials have been conducted related to the duration of storage of transfused RBCs and outcomes. Therefore, we do not know if increased duration of storage is a cause of adverse outcome. However, our data suggest that an association study, such as ours, may not be able to prove a causal relationship. Indeed, a significant limitation of our study is that patients who received RBCs stored for a prolonged duration were also more likely to have received a larger number of total RBC transfusions. Our statistical analysis included multivariate analyses that controlled for many of the potential confounders; however, we cannot exclude the potential effect of confounders.

Another limitation of our study is that it was not designed to address potential mechanisms for the putative deleterious effects of prolonged storage of RBCs. Our results, however, are consistent with a number of authors who have shown storage-induced changes in blood, e.g., decreases in RBC deformability (8,25). The transfusion of rigid and abnormally shaped RBCs may lead to decreased microcirculatory blood flow, tissue hypoxia, and, potentially, MOF and death (8). In addition, Stadler et al. (26) showed that altered RBC membranes serve as thrombogenic surfaces for platelet activation and increased procoagulant activity, which has been linked to MOF, stroke, pulmonary embolism, or other catastrophic events (27,28). Further limitations of this study include its retrospective nature and the fact that it is a single-center study, and these findings may not be generalizable to other centers.

Despite the inherent limitations of our study, we observed a robust association between the duration of storage of transfused RBCs and mortality, ARD, and ICU and hospital LOS after repeat cardiac surgery. The clinical significance of duration of storage of RBCs should be investigated in a large, randomized, blinded clinical trial.

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