Effect of duration of red blood cell storage on early and late mortality after coronary artery bypass grafting

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Objectives: Recently, concern has been expressed about the transfusion of older red blood cells after cardiac surgery. We tested the hypothesis that longer storage of transfused red blood cells increases the risk of early and late mortality in patients who undergo coronary artery bypass grafting.

Methods: We retrospectively analyzed data of patients who underwent isolated coronary artery bypass grafting between January 1998 and December 2007 in Catharina Hospital, Eindhoven, The Netherlands, and received up to 10 U of red blood cells intraoperatively or during the first 5 postoperative days. The patients were divided into 3 groups according to the storage time of the red blood cells, with a cutoff point of 14 days, as follows: “only younger blood” (n = 1422), “only older blood” (n = 1719), and at least 1 U of older RBCs (“any older blood”; n = 2175).

Results: The mean follow-up time was 1693 ± 1058 days (range, 0–3708 days). The median follow-up time was 1629 days. Univariate and multivariate logistic regression analyses revealed that the number of transfused units but not the storage time of blood entered either as a continuous variable or as a dichotomous variable with a cutoff point of 14 days was a risk factor for early mortality. Neither the number of transfused units nor the storage time was an independent risk factor for late mortality. Log-rank testing revealed no statistical difference in survival among the groups.

Conclusions: The storage time of transfused red blood cells is not a risk factor for early or late mortality in patients who undergo coronary artery bypass grafting. (*J Thorac Cardiovasc Surg* 2011;141:231-7)

Critically ill patients, including those who undergo cardiac surgery, experience more severe complications if they receive blood transfusions.¹⁻³ The storage time of red blood cells (RBCs) might affect the risk of experiencing those complications⁴⁻¹² because RBCs undergo structural and functional changes that reduce function and viability after transfusion.¹²⁻¹⁶ Recently, some,^{17,18} but not all,¹⁹⁻²¹ investigators have expressed their concern about using older RBCs for transfusion during or after cardiac surgery. In those reports several end points in heterogeneous patient populations were mentioned. We therefore investigated whether longer storage of transfused RBCs

increased the risk of early or late mortality in a large group of patients who underwent coronary artery bypass grafting (CABG) at a single medical center.

MATERIALS AND METHODS

Patients

This study included the data of all adult patients (age ≥ 18 years) who underwent isolated CABG in a single medical center at Catharina Hospital, Eindhoven, The Netherlands, between January 1998 and December 2007. Clinical data (including demographic information, risk factors, and complications) from January 1998 through December 2007 were collected in a database. All patients who received between 1 and 10 U of RBCs intraoperatively or during the first 5 postoperative days were included in this study. Patients who received more than 10 U of RBCs during that period were excluded.

Approval was obtained from the institution's research review board before the initiation of the study. Data concerning blood transfusions and the storage time of RBCs were collected from the database of the hospital transfusion service. For every patient, the maximum storage time of the transfused RBCs was used for analysis. The patients were divided into 3 groups according to the storage time of the RBCs they received: the “only younger blood” group (n = 1422), the “only older blood” group (n = 1719), and those who received at least 1 U of older RBCs (the “any older blood” group, n = 2175). The cutoff point for duration of storage of RBCs was 14 days. In this study “younger blood” refers to RBCs younger than 14 days, and “older blood” refers to RBCs older than 14 days. Patients in the only older RBCs group were also included in the any older RBCs group. Leucocyte reduction was performed for all RBC units before storage and within 24 hours after donation. RBCs were reconstituted with SAG-mannitol to a hematocrit value of 60% ± 5%, which enabled a maximum storage time of 35 days.

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Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
COPD	= chronic obstructive pulmonary disease
CrCl	= creatinine clearance
ECC	= extracorporeal circulation
EF	= ejection fraction
FFP	= fresh frozen plasma
PVD	= peripheral vascular disease
RBC	= red blood cell
2,3-DPG	= 2,3-Diphosphoglycerate

Operative Techniques

All patients received short-acting anesthetic drugs to facilitate early extubation. Normothermic extracorporeal circulation (ECC) was performed with nonpulsatile flow. According to the surgeon's preference, either cold intermittent crystalloid cardioplegia (St Thomas' solution) or intermittent warm blood cardioplegia was used to induce and maintain cardioplegic arrest. All patients who underwent CABG with the use of ECC received low-dose aprotinin (2 million KIU) during ECC that was administered in the prime solution of the ECC. (This was the regular practice in Catharina hospital in which the procedure was performed.) Patients who underwent off-pump surgery did not receive aprotinin.

During the study period, we have maintained the same policy regarding preoperative antiplatelet drugs and oral anticoagulants. Patients continued the use of aspirin until the day before the operation. Clopidogrel was discontinued 5 days preoperatively, and warfarin was discontinued 3 days preoperatively.

Follow-up Data

Follow-up data on the mortality of the patients studied were gathered from the databases of Dutch health insurance companies. Initially, the data of 9% of the total patient group could not be retrieved from those databases. To obtain mortality data for those patients, we contacted the appropriate general practitioners (or, if necessary, the authorities) of the cities in which the patients lived at the time of their operation. Early mortality was defined as death within 30 days postoperatively or death at any time if the patient did not leave the hospital or a transfer tertiary hospital alive, whereas late mortality was defined as any-cause mortality at later than 30 days postoperatively.

Statistical Analyses

Discrete variables were compared with the χ^2 test and are presented as numbers and percentages. Continuous variables were compared with the *t* test and analysis of variance and are presented as the mean $\pm$ standard deviation. Univariate and multivariate logistic regression analyses were performed to investigate the effect of biomedical variables on early mortality. Multivariate analyses were used to test for the potentially confounding effects of biomedical and demographic factors on outcome. Cox proportional hazard regression analyses were performed for the same analyses of late mortality. If they were statistically significant at a *P* value of less than .05, confounders were included in the multivariable logistic and Cox regression analyses. Factors that were statistically significant in the univariate analyses were entered in a multivariate model together with items of interest (the number of transfused blood components and the maximum storage time per blood component as a continuous variable and as a dichotomous variable). Long-term survival was described with the Kaplan-Meier method. The comparison of long-term survival in the study groups was performed

with log-rank statistics. The zero time point indicates the time of CABG. Hazard ratios with 95% confidence intervals are reported. All statistical analyses were performed with SPSS software (version 15.0; SPSS, Inc, Chicago, Ill).

RESULTS

During a 10-year period (January 1998 through December 2007), 10,626 adult patients underwent isolated CABG in Catharina Hospital, Eindhoven, The Netherlands. A total of 3597 patients received at least 1 U of RBCs perioperatively and were included in this study. After 122 patients who were lost to follow-up were excluded, we found that 1422 of the remaining patients received younger RBCs (the only younger blood group), 2175 patients received at least 1 U of older RBCs (the any older blood group), and 1719 patients received older RBCs (the only older blood group). The mean follow-up time was 1693 ± 1058 days (range, 0–3708 days), with 0 days for operative deaths. The median follow-up time was 1629 days.

The baseline characteristics of the patients who received only younger blood, any older blood, and only older blood are shown in Table 1. Patients who received only younger blood were relatively younger (66.7 vs 67.6 years), more often had chronic obstructive pulmonary disease (COPD; 14.7% vs 12%), and had a higher preoperative hemoglobin level (13.2 vs 12.9 g. dL⁻¹) than did patients of the any older blood or only older blood groups. In the only older blood group of patients, the number of grafts was higher (3.4 vs 3.5), but the percentage of re-exploration was less (11.7% vs 9.0%). The number of transfused RBC units was higher in the any older blood group than in the only younger blood group and lower in the only older blood group than in the only younger blood group. The number of transfused units of fresh frozen plasma (FFP) and platelets were highest in the any older blood group. Late mortality occurred more often in patients who received younger blood, but no difference was found in the incidence of early mortality among the 3 groups (Table 2).

Risk factors for early mortality identified by means of univariate logistic regression analysis and for late mortality identified by means of Cox regression analyses are shown in Table 3. When the maximum storage time was used as a continuous variable, having received at least 1 U of older RBCs or only older blood was not identified as a risk for either early or late mortality. However, the number of transfused units of RBCs, FFP, and platelets were significant for both early and late mortality.

Other risk factors for early mortality were age, female sex, COPD, diabetes, low creatinine clearance (CrCl), a left ventricular ejection fraction (EF) of less than 35%, a low preoperative hemoglobin level, previous cardiac surgery, peripheral vascular disease (PVD), emergency operation, perioperative myocardial infarction, or re-exploration for any cause. For late mortality, the risk factors were age,

TABLE 1. Baseline characteristics stratified by the duration of storage of RBCs

	Only younger RBCs (n = 1422)	Any older RBCs (n = 2175)	P value	Only older RBCs (n = 1719)	P Value
Preoperative factors*					
Age (y)	66.7 ± 9.4	67.6 ± 9.2	.06	67.6 ± 9.2	.011
Male sex	847 (59.6)	1244 (57.2)	.167	977 (56.8)	.127
Diabetes	327 (23.0)	499 (22.9)	.968	401 (23.3)	.832
Hypertension	601 (42.3)	951 (43.7)	.390	772 (44.9)	.139
COPD	209 (14.7)	270 (12.4)	.050	207 (12.0)	.030
PVD	179 (12.6)	307 (14.1)	.195	244 (14.2)	.208
Left ventricular EF <35%	73 (5.3)	87 (4.2)	.137	65 (4.0)	.080
CrCl	64.0 ± 21.1	63.1 ± 21.6	.233	63.6 ± 21.6	.669
Emergency operation	105 (7.4)	176 (8.1)	.447	119 (6.9)	.626
Hb (g.dL ⁻¹)	13.2 ± 1.3	12.9 ± 1.4	<.0001	13.0 ± 1.4	<.0001
Redo cardiac surgery	142 (10.0)	198 (9.1)	.382	137 (8.0)	.051
Perioperative factors					
No. of grafts	3.4 ± 1.1	3.4 ± 1.1	.054	3.5 ± 1.1	.019
Off-pump surgery	60 (4.2)	94 (4.3)	.933	78 (4.5)	.727
ECC time	64.2 ± 33.5	64.0 ± 32.1	.864	63.0 ± 30.8	.314
Re-exploration	167 (11.7)	263 (12.1)	.793	154 (9.0)	.011
Perioperative MI	71 (5.0)	123 (5.7)	.407	83 (4.8)	.868
No. of RBC units	2.6 ± 1.5	2.8 ± 1.7	<.0001	2.4 ± 1.4	.004
No. of FFP units	0.42 ± 1.15	0.54 ± 1.30	.005	0.40 ± 1.08	.579
No. of platelet units	0.06 ± 0.30	0.10 ± 0.39	<.0001	0.08 ± 0.35	.075

RBC, Red blood cell; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; EF, ejection fraction; CrCl, creatinine clearance; Hb, hemoglobin level; ECC time, duration of extracorporeal circulation; MI, myocardial infarction; FFP, fresh frozen plasma. *Results are expressed as the mean ± standard deviation or as numbers (percentages).

female sex, COPD, diabetes, low CrCl, a left ventricular EF of less than 35%, a lower preoperative hemoglobin level, previous cardiac surgery, PVD, hypertension, the number of grafts, perioperative myocardial infarction, re-exploration, the use of ECC, and the year of operation.

All risk factors identified by means of univariate analyses were entered into the multivariate logistic regression and the multivariate Cox regression model. The results are shown in Table 4. When the maximum storage time was used as a continuous variable, having received at least 1 U of older RBCs or only older blood was not a risk factor for early or late mortality. Predictors of early mortality were the number of RBC units, advanced age, COPD, diabetes, a left ventricular EF of less than 35%, and perioperative myocardial infarction. The numbers of units of FFP and platelets were not significant predictors of late mortality. Predictors of late mortality were advanced age, male sex, COPD, diabetes, low CrCl clearance, a left ventricular EF of less than 35%, a lower preoperative hemoglobin level, PVD, hypertension, and perioperative myocardial infarction. The survival curves of

patients who received a transfusion of younger blood or at least 1 U of older RBCs (Figure 1) and those who received younger blood or only older blood (Figure 2) were similar, with *P* values of .269 and .806, respectively.

DISCUSSION

In this retrospective analysis of 3597 patients who received a transfusion of RBCs during or after CABG, the storage time of the transfused RBCs was not a significant predictor of early or late mortality. The effect of the transfusion of stored blood on the outcomes of patients who undergo cardiac surgery remains controversial.¹⁷⁻²¹ That controversy might be due to the various patient populations studied, differences in study design or analysis, or different methods of blood storage. Vamvakas and Carven¹⁹ studied the effect of the length of blood storage on postoperative morbidity in 268 consecutive patients who received a blood transfusion after CABG. Those authors found no association between the age of the transfused blood and the incidence of postoperative morbidity according to

TABLE 2. Early and late mortality stratified by the duration of storage of RBCs

	Younger RBCs group (n = 1422)	Any older RBCs group* (n = 2175)	P value	Only older RBCs group* (n = 1719)	P value
End point					
Early mortality	52 (3.7%)	16 (4.9%)	.096	67 (3.9%)	.778
Late mortality	258 (18.1%)	327 (15.0%)	.014	235 (13.7%)	.001

RBC, Red blood cell. *Compared with the younger RBCs group.

TABLE 3. Univariate logistic regression analyses of risk factors for early mortality and Cox regression analyses for late mortality

Risk factors	Early mortality		Late mortality	
	Odds ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Preoperative factors				
Age (y)*	1.086 (1.067–1.105)	<.0001	1.091 (1.083–1.099)	<.0001
Male sex	0.70 (0.52–0.94)	.019	0.85 (0.75–0.97)	.021
COPD	2.05 (1.49–2.82)	<.0001	1.94 (1.68–2.23)	<.0001
Diabetes	1.42 (1.05–1.91)	.023	1.73 (1.52–1.96)	<.0001
Preoperative CrCl*	0.965 (0.959–0.972)	<.0001	0.967 (0.964–0.970)	<.0001
Left ventricular EF <35%	5.90 (4.00–8.71)	<.0001	2.64 (2.10–3.31)	<.0001
Preoperative Hb*	0.725 (0.662–0.795)	<.0001	0.731 (0.702–0.761)	<.0001
Redo cardiac surgery	3.40 (2.37–4.87)	<.0001	1.60 (1.32–1.94)	<.0001
PVD	1.58 (1.11–2.25)	.012	2.29 (1.98–2.64)	<.0001
Emergency operation	5.69 (3.98–8.14)	<.0001	1.27 (0.98–1.66)	.071
Hypertension	0.97 (0.70–1.21)	.630	1.22 (1.08–1.37)	.001
Perioperative and postoperative factors				
No. of grafts*	0.956 (0.850–1.076)	.457	1.084 (1.031–1.140)	.002
Perioperative MI	6.00 (4.03–8.94)	<.0001	1.82 (1.37–2.42)	<.0001
Re-exploration	4.50 (3.17–6.39)	<.0001	1.39 (1.11–1.75)	.004
Off-pump surgery	0.73 (0.43–1.24)	.251	0.68 (0.52–0.89)	.005
Year of operation*	0.959 (0.915–1.005)	.077	0.961 (0.934–0.989)	.006
Maximum storage of RBCs per patient*	1.017 (0.991–1.045)	.206	1.013 (0.999–1.027)	.071
Any older RBCs	1.35 (0.96–1.89)	.083	1.03 (0.87–1.21)	.714
Only older RBCs	1.06 (0.73–1.54)	.725	0.96 (0.80–1.14)	.665
No. of FFP units*	1.378 (1.262–1.505)	<.0001	1.143 (1.075–1.215)	<.0001
No. of platelet units*	2.360 (1.812–3.075)	<.0001	1.295 (1.005–1.668)	.046
No. of RBC units*	1.441 (1.374–1.511)	<.0001	1.162 (1.131–1.193)	<.0001

CI, Confidence interval; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; EF, left ventricular ejection fraction; Hb, hemoglobin level; PVD, peripheral vascular disease; MI, myocardial infarction; RBCs, red blood cells; FFP, fresh frozen plasma. *Entered as a continuous variable.

the length of intensive care treatment or hospital stay. Similar results were demonstrated by van de Watering and colleagues,²⁰ who could not show an effect of RBC storage time on mortality and morbidity in their analysis of 2732 patients who had undergone CABG. However, those authors did not exclude the negative effect of older blood on postoperative infection.²⁰ Koch and associates¹⁷ and Basran and coworkers¹⁸ found that the transfusion of older RBCs was a risk factor for various complications and increased early mortality after cardiac surgery. In the study by Koch and associates,¹⁷ more patients who received older blood exhibited preoperative mitral regurgitation, left ventricular dysfunction, and PVD. In our study the baseline characteristics of the groups studied were similar; this rendered confounding effects unlikely. By using multivariate analysis, we excluded the possible negative effects of those risk factors.

Our retrospective analysis was designed to minimize the effects of other confounding variables on early and late outcome. First, we only studied patients who underwent CABG because the complexity of the surgical procedure can affect both early and late outcomes. Other studies included patients who underwent valve surgery¹⁷ or redo surgery.¹⁸

Second, we excluded patients who received more than 10 U of RBCs (0.5% of the total CABG population). The need

for such a large number of transfused blood units reflects a major complication or a possible surgical catastrophic event. Those patients usually have a higher incidence of morbidity, mortality, or both. The poor outcomes in such cases cannot be attributed only to the storage time of transfused RBCs. Furthermore, in addition to the 2 groups who received only younger blood or only older blood, we also examined a third group of patients: those who received at least 1 U of old RBCs (the any older blood group). In that way we tested the hypothesis that having received any number of units of older RBCs can affect outcome. The absence of a significant difference in early and late mortality disproves that hypothesis. We arbitrarily dichotomized our study population into groups with a cutoff point of 14 days. Koch and associates¹⁷ used the same storage time (14 days) to define their “newer blood” and “older blood” groups. van de Watering and colleagues²⁰ used a storage time of 18 days. Other authors have used storage time as a continuous variable in their study analyses.^{18,21} These factors can also explain the controversy that exists concerning the effect of storage time on prognosis.

It has been assumed that preserved RBCs undergo functional and structural changes that begin after 2 weeks of storage.^{13–16} The deformability of RBCs reduces with longer storage time; this leads to reduced microvascular flow.^{13,14}

TABLE 4. Results of multivariate logistic regression analyses for early mortality and Cox regression analyses for late mortality

Risk factors	Early mortality		Late mortality	
	OR (95% CI)	P value	HR (95% CI)	P value
Max ST RBCs*	1.000 (0.969–1.032)	.994	1.007 (0.993–1.023)	.330
Any older RBCs	1.13 (0.76–1.66)	.529	1.02 (0.85–1.22)	.763
Only older RBCs	1.02 (0.67–1.56)	.894	1.01 (0.83–1.23)	.872
No. of RBC units*	1.262 (1.125–1.416)	<.0001	1.010 (0.947–1.077)	.764
No. of FFP units*	0.863 (0.721–1.033)	.109	1.056 (0.956–1.165)	.282
No. of platelet units*	1.321 (0.832–2.097)	.238	1.027 (0.725–1.454)	.882
Age (y)*	1.065 (1.035–1.097)	<.0001	1.051 (1.036–1.066)	<.0001
Male sex	1.40 (0.93–2.12)	.102	1.68 (1.28–2.03)	<.0001
COPD	2.20 (1.43–3.37)	<.0001	1.91 (1.55–2.37)	<.0001
Diabetes	1.60 (1.06–2.41)	.023	1.39 (1.14–1.69)	.001
CrCl*	0.991 (0.979–1.003)	.124	0.980 (0.974–0.986)	<.0001
Left ventricular EF <35%	4.74 (2.71–8.27)	<.0001	1.95 (1.37–2.77)	<.0001
Preoperative Hb*	1.024 (0.896–1.171)	.726	0.813 (0.759–0.870)	<.0001
Redo cardiac surgery	1.11 (0.61–2.00)	.726	1.17 (0.87–1.56)	.290
PVD	1.22 (0.76–1.98)	.400	1.54 (1.24–1.92)	<.0001
Emergency surgery	1.86 (0.85–4.03)	.116		
Hypertension			1.20 (1.00–1.43)	.044
No. of grafts			0.974 (0.894–1.062)	.553
Perioperative MI	4.33 (2.56–7.35)	<.0001	1.90 (1.31–2.75)	.001
Re-exploration	1.62 (0.90–2.89)	.101	1.29 (0.91–1.81)	.141
Off-pump surgery			0.78 (0.43–1.41)	.418
Year of operation			0.934 (0.892–0.978)	.004

OR, Odds ratio; CI, confidence interval; HR, hazard ratio; Max ST RBCs, maximum storage time of red blood cells per patient; RBCs, red blood cells; FFP, fresh frozen plasma; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; EF, ejection fraction; Hb, hemoglobin level; PVD, peripheral vascular disease; MI, myocardial infarction. *Entered as a continuous variable.

Oxygen delivery capacity of the stored RBCs is also reduced because of the depletion of 2,3-diphosphoglycerate (2,3-DPG).²² The transfusion of stored rigid RBCs with low oxygen transport capacity could thus impede blood flow and predispose the patient to ischemia. Our study does not support that hypothesis because we found that the effect of a transfusion of older blood on mortality was not significant. It is possible that the effect of storage of RBCs on oxygen delivery is only physiologically significant, reversible, or insufficient to affect mortality. After transfusion, 2,3-DPG levels usually normalize within a few days.²³ Tinmouth and Chin-Yee²⁴ indicated that the transfusion of 2,3-DPG-depleted blood in human subjects and animals produced no impairment in work performance, mortality, or tolerance of hypoxemic conditions. In addition, various storage conditions can retard the deterioration of RBCs. Van de Watering and colleagues²⁰ did not find an association between the storage time of RBCs and adverse outcome after CABG, and their results confirm those of our study. Differences in blood-withdrawal techniques, processing, and storage protocols for blood components among countries might explain the varying results. The protocol for the preservation of RBCs in The Netherlands seems to be safe for patients who need a transfusion of RBCs after CABG.

We suggest that the possible harm caused by the transfusion of stored RBCs must be weighed against the clinical

benefits of transfusion. Prospective randomized studies are needed to determine the significance of storage effects of transfused RBCs after CABG. However, this is unlikely to occur because of the general shortage of blood for transfusion, logistical difficulties, and ethical issues worldwide.

Study Limitations

In this retrospective study other factors that are unaccounted for in the described demographic characteristics might have caused the differences cited. A prospective randomized trial could eliminate that shortcoming. Unfortunately, we were not able to report the causes of death in the study subjects. The study end point was all-cause mortality. No data were addressed about postoperative complications, such as pulmonary or renal complications, prolonged hospital stay, or postoperative infections. Except for patients undergoing off-pump coronary artery bypass, other patients received aprotinin, which might reduce the need for transfusion and hence early outcome.²⁵ Our study is, to our knowledge, the second single-center study on the effect of storage time of RBCs after CABG that has been performed in The Netherlands. Whether the results of Dutch studies apply to patients undergoing CABG in countries in which other types of blood-withdrawal, processing, and storage protocols of RBCs are implemented remains to be investigated.

FIGURE 1. Kaplan–Meier curves and storage times of red blood cells (RBC) in patients who received only younger RBCs and those who received at least 1 U of older RBCs.

FIGURE 2. Kaplan–Meier curves and storage times of red blood cells (RBC) in patients who received only younger RBCs and those who received only older RBCs.

CONCLUSIONS

In a group of 3597 (of a total of 10,626) patients who received between 1 and 10 U of RBCs within the first 5 post-operative days after CABG, we found a clear correlation between the number of transfused RBCs and early mortality. The storage time of RBCs was not a predictor of early or late mortality.

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