Does the storage time of transfused red blood cells influence regional or global indexes of tissue oxygenation in anemic critically ill patients?*

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Objective: **To determine whether transfusion of red cells either ≤5 days or ≥20 days from donation alters tonometric indexes of gastric mucosal oxygenation or global oxygenation parameters in euvolemic anemic critically ill patients without ongoing hemorrhage. The *a priori* hypothesis was that stored red cells worsen gastric oxygenation.**

Design: **Prospective, double-blind, randomized study.**

Setting: **A 12-bed general medical/surgical intensive care unit in a Scottish teaching hospital.**

Patients: **Ventilated euvolemic anemic (mean ± SD hemoglobin, 85.8 ± 8.4 g/L) critically ill patients with significant organ failure, but no evidence of hemorrhage.**

Interventions: **After baseline measurements, patients were randomized to receive two units of leukodepleted red cells that were either ≤5 days (ten patients) or ≥20 days (12 patients) after donation according to a standardized protocol.**

Measurements and Main Results: **Changes in gastric to arterial Pco_2 gap (Pg-$Paco_2$ gap), gastric intramucosal pH, arterial pH, arterial base excess, and arterial lactate concentrations were measured during baseline (2.5 hrs), during transfusion (3 hrs), and for 5 hrs after transfusion. Mean age of red cells stored ≤5 days was 2 days (first and third quartile, 2, 2.25; range, 2–3); red cells stored ≥20 days had a mean age of 28 days (first and third quartile, 27, 31; range, 22–32). Hemoglobin concentration increased by 15.0 g/L and 16.6 g/L, respectively, in the fresh and stored groups ($p = .62$). There were no significant differences between the groups either using treatment-by-time analysis or comparing the pre- and posttransfusion periods either for Pg-$Paco_2$ gap (mean difference, 0.03 kPa; 95% confidence limits, −1.66, 1.72) or gastric intramucosal pH (mean difference, 0.015 pH units; 95% confidence limits, −0.054, 0.084). The mean change within each group from the pre- to posttransfusion period for Pg-$Paco_2$ gap and gastric intramucosal pH, respectively, was 0.56 kPa (95% confidence limits, −0.68, 1.79) and −0.018 pH units (95% confidence limits, −0.069, 0.032) for "fresh" red cells and 0.52 kPa (95% confidence limits, −0.6, 1.64) and −0.033 pH units (95% confidence limits, −0.080, 0.129) for "stored" red cells. There was no statistically or clinically significant improvement in any other oxygenation index during the measurement period for either group compared to baseline values.**

Conclusions: **Transfusion of stored leukodepleted red cells to euvolemic, anemic, critically ill patients has no clinically significant adverse effects on gastric tonometry or global indexes of tissue oxygenation. These findings do not support the use of fresh red cells in critically ill patients. (Crit Care Med 2004; 32:364–371)**

KEY WORDS: blood transfusion; critical illness; oxygenation; gastric tonometry; anemia; storage lesion

Our understanding of the best way to optimize oxygen delivery in the critically ill has changed significantly in recent years. The traditional view that supranormal levels of oxygen delivery should be maintained using inotropic drugs and red cell transfusions has been replaced by randomized, controlled trial evidence that supranormal goal-directed therapy does not improve outcome in patients with established critical illness (1) and might have adverse effects (2). Another randomized, controlled trial (the Transfusion Requirements in Critical Care study) comparing a liberal transfusion strategy (hemoglobin transfusion trigger >100 g/L) with a restrictive strategy (hemoglobin transfusion trigger 70, maintaining level at 70–90 g/L) further supported this finding by showing a trend toward improved outcome in the restrictive group, particularly in patients who were younger and less severely ill (3). This study raised the possibility that anemia is beneficial during critical illness and/or that transfusion of stored red cells has adverse effects (4). In contrast, a recent randomized, controlled trial of early goal-directed therapy in patients with early sepsis found improvements in outcomes, including mortality, when a protocol that included liberal transfusion practice to keep hematocrit ≥30% was used (5). Recent large cohort studies in

***See also p. 594.**

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European (6), Australian (7), U.S. (8), Scottish (9), and London (UK) (10) intensive care units (ICUs) indicate that mean hemoglobin transfusion thresholds are typically 85 g/L since publication of these studies.

If red cell transfusion has adverse effects, these might be due to transfusion of donor leukocytes or because of depletion of red cell 2, 3 diphosphoglyceric acid (DPG) and ATP and changes to the red cell membrane that reduce cell deformability (11). This "storage lesion" could impair oxygen delivery to tissues by reducing both capillary flow and oxygen unloading from hemoglobin. There are remarkably few data in humans regarding the importance of the red cell storage lesion, but many clinicians believe that fresh red cells are more likely than stored cells to benefit patients (12, 13). One study supporting this view is an oxygen kinetics study that retrospectively found a correlation between the transfusion of red cells stored for >15 days and a deterioration in gastric intramucosal pH (pHi), an index of gastric oxygenation status (14). This study is frequently cited as evidence for a detrimental effect of stored red cell transfusion, despite controversy surrounding the clinical relevance of tonometry-derived oxygenation indexes. Another study in oxygen supply-dependent rats found that red cells stored for 28 days, in contrast to fresh red cells, did not reverse oxygen supply dependency (15), although this may have been because of low rat red cell survival after storage (16). There are no prospective, randomized studies in humans that compare the effect of fresh and stored red cells on indexes of tissue hypoxia in critically ill humans. This is, in part, because a protocol randomizing patients to receive fresh or stored red cells is complex to organize and requires close collaboration between clinicians and the blood bank.

Many blood transfusion services have recently added universal leukodepletion to the routine processing of all blood components. The previously cited studies all used nonleukodepleted red cells or whole blood. These may have different effects on patients from the current product that is leukofiltered, plasma depleted, and resuspended in additive solution. There are no data regarding the effect of transfusing leukodepleted red cells on indexes of tissue hypoxia in critically ill patients. We therefore carried out an exploratory double-blind, prospective, randomized study to determine whether the age of transfused leukodepleted red cells influenced indexes of regional (gastric mucosal) oxygenation or clinically relevant global indexes of tissue hypoxia.

MATERIALS AND METHODS

Setting. The study took place between November 1999 and December 2000 in a single teaching hospital general ICU. The unit was a 12-bed tertiary referral center admitting 650 patients annually.

Study Aims. Our primary aim was to determine whether the age of leukodepleted red cells influenced gastric tonometry indexes of gastric mucosal oxygenation during or after transfusion to critically ill patients who had no evidence of acute bleeding. Our secondary aims were to determine whether the age of transfused red cells influences arterial acid-base status and lactate concentration.

Size of Study. The study was an exploratory investigation to assess whether the age of transfused red cells had a clinically significant effect on the above oxygenation indexes. We also planned to assess the number of patients who would need to be studied to prove various levels of difference in these indexes between the groups. We chose to randomize 22 patients to ensure ten patients per group. This number was chosen pragmatically based on a) the supposition that if the effect observed by Marik and Sibbald (14) were reproduced, it might be apparent in a study this size and b) the estimation that given the complex organizational issues involved in randomization and blinding, the study would be completed in 12 months.

Patients. All ICU patients were screened daily for inclusion in the study. Inclusion criteria were a) the intensive care physician caring for the patient had decided to transfuse two units of red cells to increase the hemoglobin concentration in the absence of clinically obvious bleeding; b) transfusion could be deferred 12–18 hrs to enable relatives' assent to be sought where necessary and randomization to be done; c) hemoglobin concentration at the time of screening was ≤90 g/L; and d) patient had not received a red cell transfusion for at least 48 hrs before the baseline measurements were to start. Exclusion criteria were a) presence of clinically apparent bleeding; b) contraindication to placement of a nasogastric tube; c) patient required frequent changes in respiratory or cardiovascular support due to physiologic instability; d) patient was not expected to survive >24 hrs; e) previous gastric surgery; f) postoperative liver transplant patient; g) age ≤16 yrs; and h) pregnancy. The study had ethical approval from the regional ethics committee. Consent was obtained from patients (when feasible), or assent was sought from relatives. The severity of illness of patients was described by calculating Marshall's Organ Failure Score on the day of study entry (17) and by recording the presence of confirmed infection.

Randomization. A sample of clotted blood was sent to the blood bank for cross matching. Patients were randomized to receive either two units of leukodepleted red cells collected ≤5 days or two units collected ≥20 days before the planned start of the study transfusion. Patients were only randomized if blood of both ages was available. If patients developed exclusion criteria between screening and the planned start of the study protocol, they were excluded from the study. Random-length block randomization was carried out by the Health Services Research Unit, Aberdeen, Scotland. Nonresealable envelopes, prepared by the Health Services Research Unit, were opened for individual patients by blood bank staff only after they had established that compatible blood of each age range was available. No more than one patient was randomized per day.

Preparation and Blinding of Red Cells. Red cells were from routine blood bank stock. All donations were leukofiltered at the time of initial component preparation, plasma depleted, and suspended in SAG-M solution. During the study period, the blood bank kept a small supply of blood for each of the age ranges specifically for the purpose of the study. To ensure that all individuals in the ICU were blinded to the age of the transfused units, special blood pack labels and forms were printed for the study. These obscured the collection and expiry dates, but stated a time within which the blood must be transfused, which allowed full checking before administration.

Outcome Measures. The primary outcome measure compared between the groups was the intragastric-arterial difference in Pco_2 ($Pg-Paco_2$ gap) during and after the red cell transfusion using air tonometry. Physiologic variables that were compared as secondary outcome measures were pHi, arterial lactate concentration, $Paco_2$, arterial pH, and arterial base excess. Changes in arterial hemoglobin concentration during the study period were also compared.

To describe patients, we chose a $Pg-Paco_2$ gap >0.8 kPa as abnormal and >2 kPa as indicative of tissue hypoxia (18, 19). For pHi, we chose a value of <7.35 as abnormal (19–21).

Study Protocol. The study protocol is summarized in Figure 1. An air tonometry catheter (Tonocap, Datex-Ohmeda, Helsinki) was placed before the start of baseline measurements, and its position in the stomach was confirmed by aspiration and, if necessary, radiologically. The Tonocap is an automated device that measures the Pco_2 in gas cycled through a balloon close to the end of the modified nasogastric tube (22). Equilibration time for the gas was set at 10 mins according to the manufacturer's recommendation. A gastric luminal Pco_2 ($Pgco_2$) was measured at the end of each 10-min dwell time. All patients

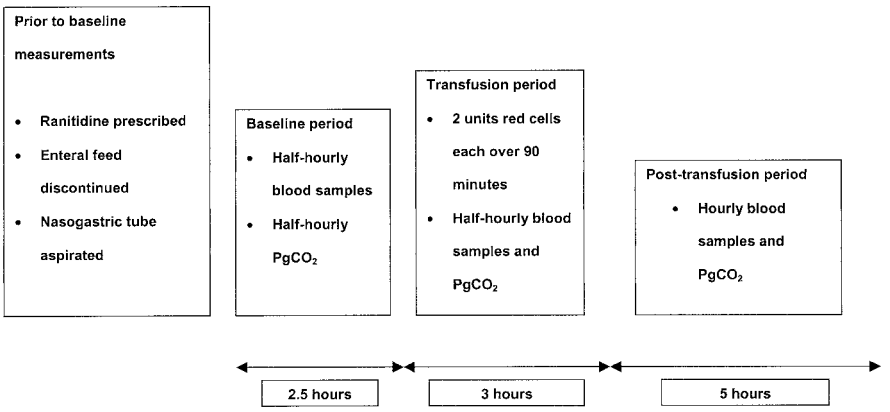

Figure 1. Summary of the study protocol.

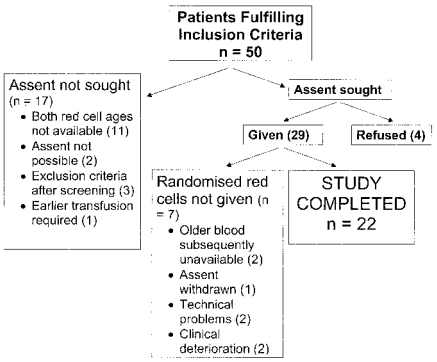

Figure 2. Description of all patients fulfilling inclusion criteria during the study period, exclusions (with reasons), and patients completing the study.

were prescribed ranitidine intravenously for the study period to improve the reproducibility of $Pgco_2$ measurements. This was administered at least 8 hrs before baseline measurements began. Patients established on enteral feeding had this discontinued at least 4 hrs before measurements started, and the absence of gastric feed was confirmed by aspiration. Feeding was restarted after the study was completed. Ventilator settings were not altered for the study, and changes were avoided during the measurement period to minimize disruption of CO_2 steady-state in the patients. Routine interventions such as physiotherapy, suctioning, and turning were avoided, but were carried out if clinically indicated. When this occurred, data were not recorded for at least 10 mins to allow steady-state to reestablish.

Blood samples were drawn at regular intervals from an arterial catheter (see Fig. 1 for timing). The following variables were measured using a Chiron 865 analyzer (Chiron Diagnostics, Newbury, UK): Pao_2, $Paco_2$, H^+, base excess, arterial whole blood lactate concentration, and hemoglobin concentration. The most recent regional CO_2 was noted at each blood sampling time point.

At the end of the baseline period, the two units of red cells were administered for 3 hrs using a controlled infusion device. The red cell units were mixed before administration and were warmed to 37°C during infusion using a blood warmer. A sample from each red cell unit was taken at the start of the infusion and sent for blood gas analysis and measurement of hematocrit. The investigator was blinded to these results.

Statistical Analysis. Each of the response variables was analysed initially using a repeated-measures analysis of variance using PROC MIXED in SAS version 8 (SAS Institute, Cary, NC). The models incorporated effects for time from the start of transfusion, treatment, treatment-by-time interaction, and the mean level of the variable during the 2.5 hrs before starting the transfusion (baseline period). After consideration of various covariance structures for repeated observations on the same subject, a Toeplitz structure was found to produce the best fit. The estimates of treatment differences after completion of the transfusion, and estimates for the change within each treatment group from pretransfusion values, were obtained with relevant ESTIMATE statements in SAS.

Because the data contained outliers for some variables, simple nonparametric methods were also applied. We used medians and quartiles for the presentation of data in tables and figures. There were no conflicts between the conclusions of the two methods of analysis used.

RESULTS

The numbers of patients fulfilling inclusion criteria, inclusions, exclusions, and the reasons for exclusion are shown in Figure 2. All patients who were randomized and received red cells were included in the analysis. Characteristics of the patients who were studied are shown in Table 1. Independent comparison of the planned randomization sequence with the actual events showed that all steps were correctly followed.

A comparison of the red cells received by the two groups is shown in Table 2. The dose of red cells administered was slightly greater in the ≥20 days old group.

Baseline Characteristics

There were no relevant differences between the groups at baseline for any of the measured physiologic end points (Table 3). In the "fresh" group 10/10 patients had a mean baseline Pg-$Paco_2$ gap >0.8 kPa, 5/10 had >2 kPa, and 7/10 had a pHi <7.35; in the "stored" group 11/12 patients had a mean baseline Pg-$Paco_2$ gap >0.8 kPa, 4/12 had >2 kPa, and 6/12 had a pHi <7.35.

Changes in Hemoglobin Concentration

Changes in hemoglobin concentration for the groups are illustrated in Figure 3. Increments in hemoglobin from baseline to the posttransfusion period were similar ($p = .62$) (Table 4)

Changes in Indexes of Tissue Hypoxia and Organ Perfusion

$Paco_2$, Pg-$Paco_2$ Gap, and pHi. There were no significant changes in $Paco_2$ during the study period either within or between the groups, indicating that total-body CO_2 steady-state was not acutely altered (Fig. 4). Baseline values for Pg-$Paco_2$ gap and pHi were abnormal in the majority of patients, but to a very variable degree (Fig. 4).

Examining treatment-by-time interactions during the 5 hrs posttransfusion period, there was no difference between the groups either for $Pgco_2$-$Paco_2$ gap ($p = .82$) or for pHi ($p = .99$). Comparing the baseline (2.5 hrs) with the posttransfusion (5 hrs) periods for Pg-$Paco_2$ gap, the mean adjusted change from pre- to posttransfusion periods for the fresh red cells was 0.56 kPa (95% confidence limits, −0.68, 1.79) and for the stored red cells was 0.52 kPa (95% confidence limits, −0.60, 1.64). The mean adjusted difference between the groups between the pre- and posttransfusion periods was 0.03 kPa (95% confidence limits, −1.66, 1.72). In the fresh group, 8/10 patients had a mean posttransfusion Pg-$Paco_2$ gap >0.8 kPa and 4/10 had >2 kPa; in the stored

Table 1. Characteristics of study patients

Patient	Sex	Age	Admission Diagnosis	Days in ICU at Time of Study	Days with Hemoglobin <90 g/L Before Study	Admission APACHE II Score	Organ Failure Score on Day of Study	Confirmed Infection at Time of Study	Enteral Feeding
Red cell transfusion ≤5 days old									
1	M	52	Multiple trauma	14	4	18	10	Y	Y
2	M	59	GI perforation	9	5	22	3	Y	N
3	M	32	Multiple trauma	8	4	18	6	Y	N
4	F	74	Bacterial pneumonia	10	2	14	6	N	Y
5	F	60	Siezures/alcoholic liver disease	2	2	29	6	Y	Y
6	M	59	GI perforation	6	3	23	10	Y	N
7	M	44	Acute pancreatitis	22	3	29	7	Y	Y
8	M	57	Bleeding oesophageal varices/ alcoholic liver disease	10	4	20	5	Y	Y
9	M	63	Acute pancreatitis	5	5	37	7	N	Y
10	F	50	Sepsis/alcoholic liver disease	7	6	31	9	Y	Y
Mean (SD)				9.3 (5.5)	3.8 (1.3)	24 (7)	6.9 (2.2)		
Red cell transfusion ≥20 days old									
1	F	67	Bacterial pneumonia	4	3	26	9	Y	N
2	F	36	GI perforation	9	4	11	1	N	Y
3	M	70	Bacterial pneumonia	14	7	18	6	N	Y
4	M	58	Bacterial pneumonia	3	0	22	6	Y	Y
5	M	68	Ruptured abdominal aortic aneurysm	3	3	30	11	N	Y
6	M	57	Multiple trauma	9	3	15	2	Y	Y
7	M	78	Bacterial pneumonia	2	3	24	7	N	Y
8	F	53	Bacterial pneumonia	4	3	17	8	Y	Y
9	M	70	Ruptured abdominal aortic aneurysm	5	2	22	5	Y	Y
10	M	56	Bacterial pneumonia	5	5	19	2	Y	Y
11	F	70	GI perforation	11	4	16	8	Y	N
12	F	43	Fulminant hepatic failure (acetaminophen)	6	3	23	10	N	N
Mean (SD)				6.3 (3.7)	3.3 (1.7)	20 (5)	6.3 (3.3)		

ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; GI, gastrointestinal.

group 11/12 patients had a mean posttransfusion Pg-$Paco_2$ gap >0.8 kPa, and 4/12 had >2 kPa.

For pHi, the mean adjusted change from pre- to posttransfusion periods for the fresh red cells was −0.018 pH units (95% confidence limits, −0.069, 0.032) and for the stored red cells was −0.033 pH units (95% confidence limits, −0.080, 0.129). The mean adjusted difference between the groups between the pre- and posttransfusion periods was 0.015 pH units (95% confidence limits, −0.054, 0.084). In the fresh group, 7/10 had a mean posttransfusion period pHi <7.35; in the stored group, 10/12 had a posttransfusion period pHi <7.35. Median (quartile) data values for Pg-$Paco_2$ gap and pHi are illustrated at all time points in Figure 4. Median (quartile) pre- and posttransfusion values are shown in Table 4.

Individual data for Pg-$Paco_2$ gap are shown in Figure 5. There was no obvious difference between patients who had normal or abnormal Pg-$Paco_2$ gap or pHi at baseline.

Lactate and Systemic Acid-Base Balance. Most patients were not acidotic or acidemic during the baseline period, but mean lactate concentrations were increased in the majority of patients before transfusion (Table 3). No acid-base parameter changed significantly between the pre- and posttransfusion periods either within each group or comparing changes between the groups (Fig. 6).

DISCUSSION

The primary aim of this study was to determine whether red cells stored for ≥20 days adversely affected indexes of gastric oxygenation in critically ill patients because this had been suggested by a *post hoc* analysis of data in a widely cited earlier study (14). We successfully randomized patients prospectively to receive leukodepleted red cells that were either fresh (stored ≤5 days) or had prolonged storage time (≥20 days). We found no evidence of clinically relevant worsening in Pg-$Paco_2$ gap, pHi, or any global measure of tissue hypoxia after transfusion of leukodepleted red cells stored for ≥20 days. There were no detectable differences in the changes that occurred with fresh or stored red cells. We were also unable to demonstrate a beneficial effect of red cell transfusion on indexes of tissue hypoxia when hemoglobin concentration was increased from about 80–90 g/L to 95–110 g/L even when very fresh red cells were transfused. Recent large cohort studies have shown that 40% to 80% of red cell transfusions in ICUs are not administered for hemorrhage, but for indications variously described as "low hemoglobin," "dimin-

Table 2. Age and characteristics of the red cell units given

	Red cells ≤5 Days (n = 10)	Red cells ≥20 Days (n = 12)
Age, days		
Median	2	28
First and third quartiles	2, 2.25	26.75, 31
Range	2–3	22–32
H^+ concentration, nmol/L	130 (9)	354 (37)[b]
Lactate concentration, mmol/L	6.63 (1.68)	21.44 (4.87)[b]
Total volume transfused, mL	542 (29)	575 (34)[a]
Hematocrit	0.57 (0.02)	0.60 (0.01)[b]
Red cell volume transfused, mL	307 (25)	344 (26)[b]
Blood group		
A^+	3	5
O^+	3	6
O^-	2	0
B^+	2	1

All values are mean (SD) unless stated.
[a] $p < .05$; [b] $p < .01$.

Table 3. Physiologic variables during baseline measurements for the groups

	Red Cell Storage ≥20 Days (n = 12)	Red Cell Storage ≤5 Days (n = 10)
Pao_2, kPa	12.42 (11.28, 13.12)	11.74 (10.75, 13.53)
$Paco_2$, kPa	5.30 (4.67, 6.29)	5.59 (4.97, 6.15)
$Pgco_2$, kPa	6.65 (6.21, 8.10)	7.34 (6.78, 9.03)
Pg-$Paco_2$, kPa	1.67 (0.94, 2.11)	1.84 (1.75, 2.16)
pHi	7.34 (7.20, 7.37)	7.30 (7.25, 7.36)
Hemoglobin, g/L	85.3 (79.9, 91.1)	84.3 (81.0, 87.6)
pHa	7.45 (7.41, 7.47)	7.45 (7.40, 7.47)
Hco_3 (actual), mmol/L	27.23 (24.10, 28.93)	29.76 (27.00, 32.37)
Base excess, mmol/L	2.57 (−0.24, 4.98)	3.8 (2.05, 7.56)
Lactate, mmol/L	1.82 (1.36, 2.46)	2.26 (1.09, 2.85)
Pao_2/Fto_2, kPa	22.97 (21.31, 26.45)	25.69 (19.86, 29.70)

All values are median (first and third quartile).

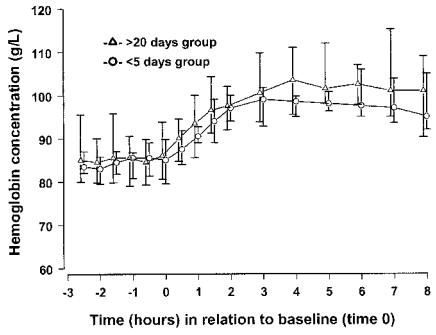

Figure 3. Changes in hemoglobin concentration during the study period. All values are median (first and third quartile). No significant differences exist between the groups.

ished physiologic reserve," or "altered tissue perfusion" (6–10). In these studies the pretransfusion hemoglobin concentrations were similar to our study. The patients studied were, therefore, typical of those who receive many red cell transfusions in the ICU, namely those with a low hemoglobin concentration, organ failure, and infection, but no evidence of hemorrhage.

Many studies of oxygen kinetics in critically ill patients have been confounded by large measurement errors in the oxygenation indexes examined together with inadequate numbers of data points (23). We collected multiple data sets during a prolonged study period so that random error was minimized. Automated gas tonometry was used in preference to saline tonometry because it has been shown to be more accurate and reproducible (19, 22). Changes to ventilation were not made, and our data indicated a stable CO_2 steady-state. Artifacts in $Pgco_2$ can result from buffering of alkali entering the stomach, but were minimized by discontinuing enteral feed and prescribing H_2-antagonists (18). During these conditions, Pg-$Paco_2$ gap is a measure of CO_2 accumulation in the gastric mucosa. This can occur because of increased CO_2 generation from increased local aerobic metabolism, buffering of lactic acid produced during anaerobic conditions, a reduction in mucosal blood flow, or a combination of these factors (24). We also calculated pHi to enable direct comparison with earlier findings and because this variable has been widely used in the critical care literature. Normal values for $Pgco_2$-$Paco_2$ gap and pHi and values that are associated with adverse clinical outcomes are not firmly established. For pHi, the most widely quoted value for the lower limit of normal is 7.35 (19). This is supported by several studies that found maximum sensitivity and specificity of this value for predicting adverse clinical outcomes, notably multiple organ failure (19–21, 25). In addition, a randomized, controlled trial found that this value delineated patients who benefited from pHi-directed oxygen delivery therapy (21). For $Pgco_2$-$Paco_2$ gap, there is less consensus regarding the upper limit of normal and the values most strongly associated with adverse outcome. A study in trauma patients found that a value of about 2.4 kPa had maximum sensitivity and specificity for predicting organ failures (25), although another study found no association between $Pgco_2$-$Paco_2$ gap and outcome in critically ill patients (26). We chose a value of 0.8 kPa as the upper limit of normal and 2 kPa as indicative of possible hypoxia based on experimental evidence and expert opinion (18). As secondary end points, we chose oxygenation indexes that are in widespread clinical use and are the best available global markers of tissue hypoxia (27).

Our randomization process successfully blinded the clinical investigators to group assignment until after the primary analysis completed by making changes to blood labels for study patients. Data from the samples taken from the red cell units were also unknown to the investigators until after the study was completed. These factors eliminated the possibility of investigator bias.

Patients receiving red cells ≥20 days from donation were transfused a slightly larger red cell volume than those in the group ≤5 days from donation. This probably occurred by chance from variation in the hematocrit and volume of donations, although some increase in red cell volume with storage occurs as a result of osmotic shifts. The difference in transfused volume between the groups (mean, 37 mL) is unlikely to have influenced our major findings. The difference in red cell storage time between the groups was ≥3

Table 4. Changes in physiologic variables from the baseline period (2.5 hrs; mean of five measurements) to the posttransfusion period (5 hrs; mean of five measurements)

	Red Cell Storage ≤5 Days (n = 10)	Red Cell Storage ≥20 Days (n = 12)
$Paco_2$, kPa	−0.15 (−0.31, −0.01)	0.02 (−0.29, 0.11)
$Pgco_2$, kPa	−0.46 (−1.36, −0.18)	0.16 (−0.36, 1.19)
$Pgco_2-Paco_2$, kPa	−0.41 (−0.82, 0.10)	0.37 (−0.17, 1.66)
pHi	0.02 (−0.01, 0.05)	−0.02 (−0.06, 0.01)
Lactate, mmol/L	0.10 (−0.16, 0.21)	0.03 (−0.10, 0.23)
pHa	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)
Hco_3^- (actual), mmol/L	−0.85 (−1.44, −0.53)	−0.29 (−0.90, 0.07)
Base excess, mmol/L	−0.70 (−1.42, −0.45)	−0.71 (−1.5, −0.42)
Hemoglobin, g/L	15.0 (11.5, 18.6)	16.6 (13.3, 19.8)

All values are median (first and third quartile). No significant differences exist between the groups.

Our data do not support the hypothesis that transfusing stored red cells adversely effects tissue oxygenation in anemic, euvolemic, critically ill patients with no evidence of bleeding.

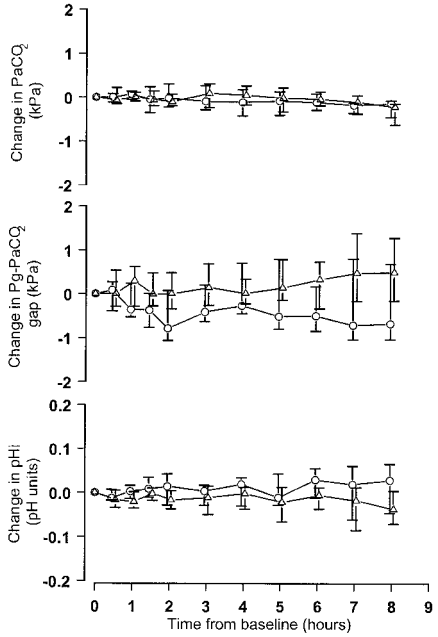

Figure 4. Changes in arterial CO_2 pressure (*$Paco_2$*), gastric to arterial Pco_2 gap (*Pg-$Paco_2$* gap), and gastric intramucosal pH (*pHi*) in relation to the mean of the values for baseline measurement period. *Circles* represent red cells ≤5 days after donation (n = 10); *triangles* represent red cells ≥20 days after donation (n = 12). All values are median (first and third quartile). No significant differences exist between the groups.

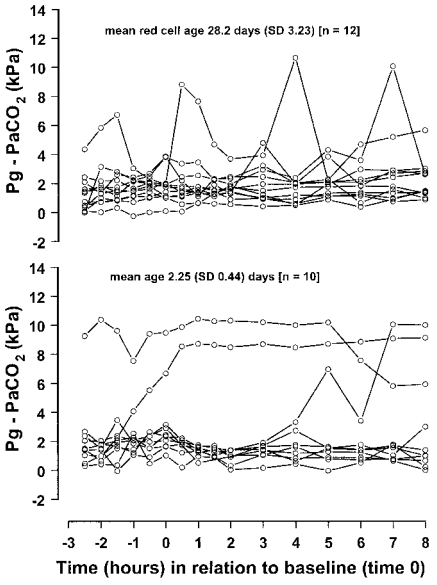

Figure 5. Individual data for gastric to arterial CO_2 gap (*Pg-$Paco_2$ gap*) during the study period for patients in the two study groups.

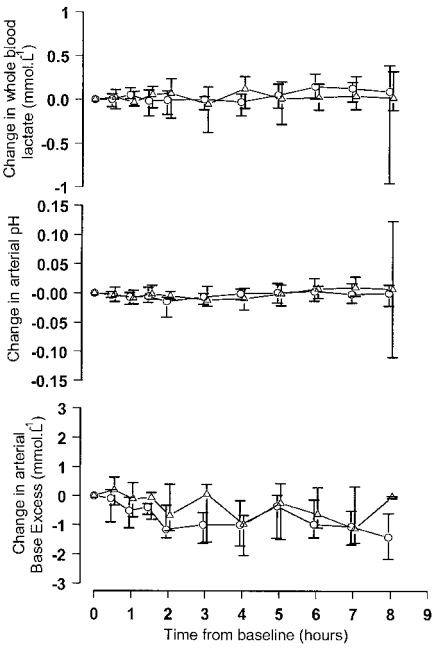

Figure 6. Changes in whole blood lactate concentration, arterial pH, and arterial base excess in relation to the mean of the values for baseline measurement period. *Circles* represent red cells ≤5 days from donation (n = 10); *triangles* represent red cells ≥20 days from donation (n = 12). All values are median (first and third quartile). No significant differences exist between the groups.

wks. In keeping with published data, lactate and hydrogen ion concentrations were significantly higher in the red cells stored ≥20 days. Red cells of this age have undergone membrane changes that result in reduced deformability and loss of the normal biconcave shape that characterizes red cells during early storage. Red cell 2,3 DPG, ATP, and hemoglobin P50 all decrease during red cell storage to an extent that is influenced by the method of processing (28). We have recently measured 2,3 DPG, ATP, and P50 in red cells that are leukofiltered and plasma reduced after donation and resuspended in SAG-M after donation, as was the case in this study and is now standard in many countries (Table 5 and S. A. McLellan, personal communication). These data show that DPG concentration is reduced by 50% even after 2 days of storage, but is completely absent in red cells stored for 28 days. These changes are accompanied by corresponding reductions in the P50 that alter the oxygen unloading characteristics of hemoglobin. In healthy volunteers, DPG regeneration occurs after 24–48 hrs and is most rapid in the first 4–8 hrs (29–31), although there are no data regarding red cell DPG recovery in critically ill patients. If these storage changes significantly impair capillary transit and oxygen unloading, we therefore expected a difference in Pg-$Paco_2$ gap between the groups during the 8-hr study period.

This was a preliminary study, and it is possible that a type II error occurred. For Pg-$Paco_2$ gap, there was no suggestion of a difference between the groups. On average, our confidence limits excluded an increase of $Pgco_2$-$Paco_2$ gap after red cell transfusion of >1.79 kPa and >1.64 kPa in the fresh and stored groups, respectively, and excluded an increase in the stored group relative to the fresh group of

Table 5. Red cell 2,3-DPG concentration, ATP concentration, and directly measured P50 in ten donated red cell units that were leukofiltered and plasma depleted after donation and resuspended in SAG-M

	Immediately After Processing (Normal Range)	2-Day Storage	28-Day Storage
2,3-DPG (μmol·gHb^{-1})	14.0 (1.7)	6.9 (3)	0 (0)
ATP (μmol·gHb^{-1})	4.6 (0.6)	4.6 (0.7)	3.6 (0.3)
P50 (kPa)	3.7 (0.2)	3.0 (0.4)	2.2 (0.1)

DPG, diphosphoglyceric acid.

Units were analyzed immediately after processing, after 2 days, and after 28 days of standard storage conditions. All values are mean (SD). Data were provided by S. A. McLellan, personal communication.

>1.72 kPa. Examining individual data (Fig. 5), few patients in either group had large changes in Pg_{CO_2}-Pa_{CO_2} gap, and in these cases, changes were not obviously related to the transfusion. We estimate that to detect a difference between the groups of 1 kPa, 29 patients in each group would need to be randomized to achieve 80% power. For pHi, on average, we could exclude a decrease in pHi after red cell transfusion of >0.079 and >0.08 pH units after fresh and stored red cells, respectively, and exclude a decrease in the stored group relative to the fresh group of >0.084 pH units. We can also make direct comparison with the study of Marik and Sibbald (14). In their nonrandomized patients, pHi decreased when blood >15 days was administered by >0.1 pH units in most patients. Our data suggest that this is an extremely unlikely response to transfusion with leukodepleted red cells stored >20 days.

There are a number of possible explanations for the difference between our data and the earlier study by Marik and Sibbald (14). First, their patients were studied earlier during sepsis and may have had greater oxygen supply dependency, making them more sensitive to impaired oxygen transport and unloading by stored red cells (32); second, we used leukodepleted red cells rather than a nonleukodepleted product; third, Marik and Sibbald transfused three units of red cells from a slightly higher pretransfusion hemoglobin threshold (mean, 90g/L) in contrast to the two units used in our study, and an adverse effect might be dose dependent; fifth, the probability of a chance association is low in a double-blind, randomized study. It is possible that the correlation found by Marik and Sibbald was not a result of cause and effect.

In conclusion, our data do not support the hypothesis that transfusing stored red cells adversely effects tissue oxygenation in anemic, euvolemic, critically ill patients with no evidence of bleeding. This contradicts the *post hoc* analysis of an earlier nonrandomized study (14). We also found no evidence of clinically measurable improvements in oxygenation parameters after fresh red cell transfusions to similar patients. Our data, therefore, do not support the routine use of fresh red cells when transfusion is necessary.

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