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Journal Title: Transfusion
Volume: Volume 55, Number 11
Publisher: Wiley: 12 months | 2015-11-01, Pages 2768-2770
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1111/trf.13276
Permanent URL: https://pid.emory.edu/ark:/25593/rs7bf

Final published version: http://dx.doi.org/10.1111/trf.13276

HHS Public Access

Author manuscript

Transfusion. Author manuscript; available in PMC 2016 November 01.

Published in final edited form as:

Transfusion. 2015 November ; 55(11): 2768–2770. doi:10.1111/trf.13276.

Effect of Storage-Aged RBC Transfusions on Endothelial Function in Healthy Subjects

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Letter to Editor

Prolonged storage of packed red blood cell units (pRBCs) is associated with biochemical changes that may cause adverse transfusion effects. These alterations include depletion of adenosine triphosphate and 2,3-diphosphoglycerate, hemolysis, formation of microparticles and oxidation of lipids amongst other metabolic and cellular disruptions.(1) These changes may produce depletion of bioavailable nitric oxide (NO) in the recipient, with subsequent endothelial dysfunction and inhibition of NO-mediated vasodilation.(1) We have previously shown that hospitalized patients receiving storage-aged RBCs (saRBCs) have significantly decreased flow-mediated dilation (FMD), indicating reduced endothelial NO activity compared to those receiving fresh RBCs (fRBCs).(2) To examine whether these effects occur in healthy subjects, we examined the impact of saRBC transfusion on FMD in healthy volunteers, with the hypothesis that impact of saRBC will differ between subjects with and without endothelial dysfunction.

In a cross-over study, 16 healthy subjects (mean age 31, 63% males, Table) donated one unit of whole blood and returned 1-7 days later to receive an autologous fRBC transfusion (<7 days of storage). Subjects later returned for the second phase of the study at least 5 days after their initial transfusion, and donated an additional unit of blood. When this unit had been stored 35-42 days, subjects were brought back and this saRBC unit was infused. Using ultrasound, brachial artery FMD was measured prior to transfusion, at 1-hour and 24-hours after both, the fRBC and saRBC transfusions.(2) FMD was calculated as (hyperemic diameter-baseline diameter)/baseline diameter*100. Statistical analysis of allometrically scaled FMD was performed using a linear mixed effects modeling for repeated measures to account for baseline diameter.(3)

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Conflict of Interest Disclosures: None of the authors have conflicts of interests to disclose.

ClinicalTrials.gov IDENTIFIER: NCT00838331
URL: www.clinicaltrials.gov/ct2/show/NCT00838331

Enrolled subjects did not have known acute or chronic illnesses with normal blood pressure and lipid profile (Table). There were no significant differences in pre-transfusion hemoglobin between the fRBC and saRBC phases of the study (12.4±1.4 versus 11.8±1.2 g/dL, respectively, P=0.1) nor post-transfusion (13.6±1.3 versus 13.4±1.2, P=0.1). Resting brachial artery diameter was similar at all time-points during each transfusion phase (Table). The pre-transfusion (8.1±7.1% versus 7.4±6.9%, respectively, P=0.9) and post-transfusion FMD measurements did not differ between the fRBC and saRBC phases (P=0.6, Figure). However, after 24-hours of saRBC transfusion, FMD was higher (7.7±3.9% versus 9.8±4.2%, P=0.019).

Thus, in healthy subjects we found no decrease in FMD with autologous saRBC compared to fRBC transfusion, suggesting NO bioavailability is not reduced in these transfusion recipients. While these findings differ from our previous results in hospitalized patients,(2) they indicate that the recipient's clinical status is likely the major determinant of whether saRBC transfusion can cause adverse effects. In support of this hypothesis, the mean FMD in our hospitalized patients was significantly lower than the current health population studied (5.1% versus 7.8%, P<0.001).(2) Zapol's studies in human transfusion recipients are in agreement, as they found no differences in the hyperemia index in nine healthy adults following fRBC versus saRBC transfusion.(4) In contrast, and consistent with our previous work, they found that obese adults with endothelial dysfunction showed significantly increased pulmonary artery pressure after transfusion of saRBC whereas transfusion of fRBC had no effects.(5) Similarly, in a number of murine,(6, 7) rat,(8) and canine (9) studies, healthy animals were relatively insensitive to effects of RBC storage age, while diseased animals (endothelial dysfunction, diabetes, pneumonia) exhibited more mortality, tissue injury, systemic hypertension, and/or inflammation after saRBC transfusion than following fRBC exposure. It is important to note that the various studies cited including our own have methodologic differences that limit drawing generalized conclusions: the number of units administered, the baseline hemoglobin, whether transfused blood was autologous or heterologous, and most importantly the subjects' demographics and clinical characteristics.

We had previously hypothesized that the cumulative effects of RBC transfusions and recipient factors are required to reduce local NO bioavailability below a critical threshold, leading to endothelial dysfunction and insufficient tissue perfusion to meet metabolic demands, and predisposing to morbidity and mortality in the transfusion recipient.(10) The present findings are consistent with this hypothesis, in that healthy recipients are unlikely to have baseline vascular dysfunction or a metabolic state that would easily be perturbed by transfusion-associated factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Sources: Support for these studies was provided by NHLBI (R01 HL095479-01, and administrative supplement to JDR), NIH grant UL1 RR025008 and the National Blood Foundation (to AR).

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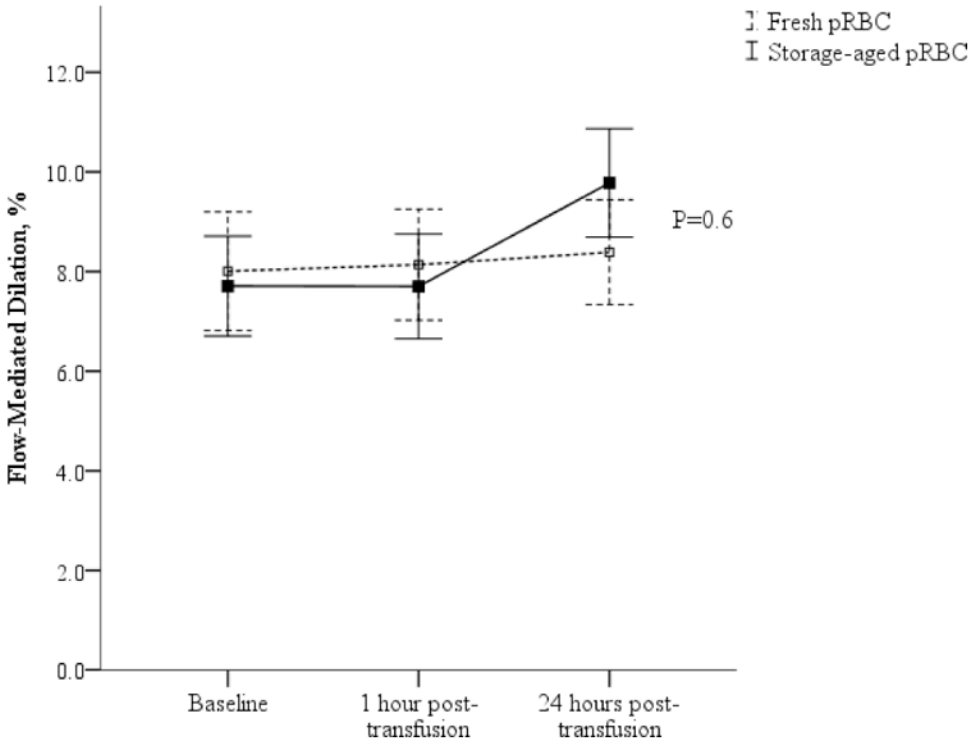

Figure.

Flow-Mediated Dilation during Transfusion of Storage-Aged and Fresh Blood Units.

pRBCs: packed red blood cells. Flow-mediated dilation (%) is adjusted for baseline brachial artery diameter using allometric scaling. P-value is for the comparison between fresh pRBC and storage-aged pRBC transfusions.

Table
Demographic and Clinical Characteristics

Variables	All Patients (n=16)
Age, years	31 (13)
Male, n (%)	10 (63%)
White, n (%)	7 (43%)
Body Mass Index, kg/m^2	26 (5)
Clinical Characteristics	
Systolic Blood Pressure, mmHg	117 (12)
Diastolic Blood Pressure, mmHg	70 (10)
Low-density Lipoprotein, mg/dL	93 (24)
High-density Lipoprotein, mg/dL	48 (9)
Fresh Blood Transfusion	
Blood Unit Storage Age, days	4 (1)
Baseline Hemoglobin, g/dL	12.4 (1.4)
Post-Transfusion Hemoglobin, g/dL	13.6 (1.3)
Baseline Brachial Artery Diameter, mm	3.3 (0.6)
1 hour Post-Transfusion Brachial Artery Diameter, mm	3.3 (0.6)
24 hours Post-Transfusion Brachial Artery Diameter, mm	3.4 (0.6)
Storage-aged Blood Transfusion	
Blood Unit Storage Age, days	38 (4)
Baseline Hemoglobin, g/dL	11.8 (1.2)
Post-Transfusion Hemoglobin, g/dL	13.4 (1.2)
Baseline Brachial Artery Diameter, mm	3.4 (0.5)
1 hour Post-Transfusion Brachial Artery Diameter, mm	3.3 (0.2)
24 hours Post-Transfusion Brachial Artery Diameter, mm	3.3 (0.6)

Values are mean (SD) or n (%) where noted.