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RESEARCH ARTICLE

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Using redox potential as a feasible marker for banked blood quality and the state of oxidative stress in stored red blood cells

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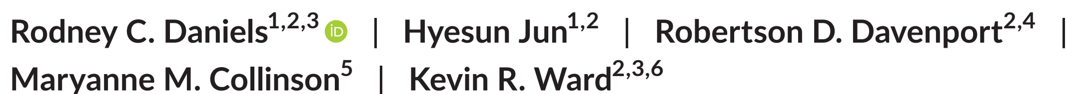

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Abstract

Background: Stored red blood cells (RBCs) may undergo oxidative stress over time, with functional changes affecting oxygen delivery. Central to these changes are oxidation-reduction (redox) reactions and redox potential (RP) that must be maintained for cell function. RP imbalance can lead to oxidative stress that may contribute to storage lesions. This study's purpose was to identify changes in RP over time in banked RBCs, and among RBCs of similar age.

Methods: Multiple random RBC segments from RBC units were tested ($n = 32$), ranging in age from 5 to 40 days, at 5-day intervals. RP was recorded by measuring open circuit potential of RBCs using nanoporous gold electrodes with Ag/AgCl reference. RP measures were also performed on peripheral venous blood from 10 healthy volunteers. RP measures were compared between RBC groups, and with volunteer blood.

Results: Stored RBCs show time-dependent RP increases. There were significant differences in Day 5 RP compared to all other groups ($p \le 0.005$), Day 10–15 vs. ages ≥ Day 20 ($p \le 0.025$), Day 20–25 vs. Day 40 ($p = 0.039$), and all groups compared to healthy volunteers. RP became more positive over time suggesting ongoing oxidation as RBCs age; however, storage time alone was not predictive of RP measured in a particular unit/segment.

Conclusions: There are significant differences in RP between freshly stored RBCs and all others, with RP becoming more positive over time. However, storage time alone does not predict RP, indicating RP screening may be an important measure of RBC oxidative stress and serve as an RBC quality marker.

KEYWORDS
blood storage lesions, oxidative stress, red blood cells, redox potential, transfusion

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1 | INTRODUCTION

Oxidation-reduction (Redox) reactions, including those involving reactive oxygen species (ROS), lie at the heart of nearly every biochemical process occurring within the body and within biologically active environments, such as that present within units of stored blood.[1,2] These redox reactions reflect the overall oxidative stress of the environment and involve the transfer of electrons between oxidants and reductants. The continuous measurement of these combined ubiquitous reactions in blood, red blood cell units (RBCs), and other biologic fluids can be termed ambient redox potential (RP). As RP is the balance of all oxidants and reductants present, it is a measure of electron pressure in the system much in the same way as pH is the measure of proton pressure (balance of acid and base) in a system. This balance may be especially important with regard to the health and viability of RBCs, with multiple manuscripts describing oxidative injury as a contributing factor in red cell storage lesions,[2-4] and evidence that the addition of antioxidant species to stored RBCs may decrease oxidative stress,[5] reduce cell damage by free radicals,[6] and preserve red cell energy, redox metabolism, and overall RBC quality.[7]

Despite the seeming importance and implications of utilizing RP measures, there are currently few means by which to make the measurement directly, and most investigators have relied historically on isolated redox species and secondary markers of oxidative stress such as glutathione couples,[8] malondialdehyde,[2] and estimates of oxidative injury in processed samples,[2,8,9] among others, instead of evaluating the state of overall oxidation-reduction balance and oxidative stress directly via measurements of RP. In addition, while measurements of oxidative stress and RP are optimally made at the bedside and/or immediately upon sample collection, few, if any, measures of redox and oxidative stress can be made at the point-of-care (POC) without sample processing. However, with the use of novel nanoporous gold electrodes our group has described previously,[10,11] we are able to make direct POC measurements of oxidative stress via RP that could provide new insight into the overall redox state, and degree of oxidative stress present in RBCs.

To this end, we report on the evaluation of RP measurements in multiple random units of RBCs by measuring RP in segments taken from banked RBCs, ranging in age from 5 to 40 days at 5-day intervals (day 5, 10, etc.), and additionally in peripheral venous blood samples taken from healthy volunteers. We sought to not only record RP measures in RBCs of varying age but also investigate whether there was a statistically significant change in oxidative stress as measured by RP (e.g., whether more oxidative or reductive) over time among stored RBCs, compare these results to the RP of peripheral venous blood of healthy volunteers, and evaluate the degree of RP variation among RBCs of similar age. We hypothesize that RP measurements will increase among RBCs overall the longer they are stored, indicating ongoing and increasing oxidation, and that the RP values of stored RBCs will be higher than that of peripheral blood of healthy volunteers.

2 | MATERIALS AND METHODS

2.1 | Blood

Red Blood Cells Additive Solution-3 (AS3) Leukocytes Reduced were obtained from the American Red Cross and stored at 1–6 C in accordance with AABB Standards.[12] A total of 32 samples of approximately 1mL were taken from segments of multiple, independent RBC units, ranging in age from 5 to 40 days at 5-day intervals, and used for testing (day 5, n = 6; 10–15, n = 8; 20–25, n = 6; 30–35, n = 9; 40, n = 3). RBC segments were selected at random, and only one measurement was made from each unit. RBCs were not tested over time and were not tested at more than one time point. In addition, 10 whole blood samples of approximately 2–3 ml were taken from 10 separate healthy adult volunteers via peripheral venipuncture and placed into sodium heparin tubes as a reference for circulating RP values in healthy individuals. After sample collection, approximately 1 ml was immediately taken for RP measurement as described below. This study was approved by the University of Michigan Institutional Review Board and informed consent was obtained from all participants in the study. The data that support the findings of this study are available from the corresponding author upon reasonable request.

2.2 | Nanoporous gold electrode fabrication and RP measurement

The nanoporous (np) gold electrode fabrication has been previously described,[10] and all electrodes utilized for this study were fabricated from the same stock and batched materials. Briefly, fabrication consists of overlaying a np gold structure onto gold coated slides, precut to an approximate dimension of 1 inch x 0.24 in. The np gold structure was obtained by dealloying gold leaf (Manetti 12 karat white gold) in nitric acid and rinsing with deionized water, which produces a complex matrix of nanopores with diameters of approximately 20–50 nm each. The combined gold slide with overlaid np structure was then treated under ultra-violet light for 4 h and the resultant np gold coated electrode was then covered with Teflon tape containing a 1/8-inch diameter hole punch in the center to provide a defined area and region for RP testing. We have previously demonstrated this electrode to have excellent intra-rater reliability, while also resistant to biofouling.[10]

Redox potential measurements were obtained and processed immediately at time of sample collection. Direct measurement of RP was performed by measuring open circuit potential of the RBC sample via the np gold electrode, with Ag/AgCl reference, using a ParstatMC™ multi-potentiostat (Princeton Applied Research). RP measurements and age of the stored RBC sample were recorded, with samples placed in one of five groups based on age. These are: (1) 5 days, (2) 10–15 days, (3) 20–25 days, (4) 30–35 days, and (5) 40 days. The RP values of blood from healthy volunteers were determined as a reference for normal circulating RP values in healthy individuals. RP measurements were not adjusted for pH.

2.3 | RP statistical analysis

Linear regression was performed on all samples collected and an R^2 value calculated, producing a fitted regression line utilizing Excel and analyzed with SAS9.4 statistical programming software (SAS Institute Inc.). In addition, Mann–Whitney *U* test with Holm Sequential Bonferroni Adjustment for multiple comparisons was used to evaluate statistical differences between the groups defined by age. The level of significance for this analysis was set at $\alpha = 0.05$, with resultant p values for group comparisons noted below.

3 | RESULTS

Median and interquartile ranges (IQR) of RP (in mV) for each group of aged RBCs tested is as follows: Day 5 = −60 (−71 to −37); Day 10–15 = 7 (−14 to 12); Day 20–25 = 33 (19 to 55); Day 30–35 = 48 (33 to 68); Day 40 = 103 (81 to 109). Samples from 10 healthy volunteers demonstrated a median of −93 mV and IQR of −105 to −78 mV. Overall, stored RBCs show time-dependent increases in RP as demonstrated in Figure 1, becoming more positive over time with a reasonable goodness of fit based on linear regression ($R^2 = 0.62$). This suggests an increase in oxidation with greater RBC storage time, and there were significant differences in Day 5 RP compared to all other groups ($p \le 0.005$). In addition, Day 10–15 RP values noted significant difference when compared to all ages ≥20 days ($p \le 0.025$), and Day 20–25 RBCs when compared to Day 40 ($p = 0.039$). All groups were noted to have a significantly more positive RP measurement when compared to peripheral venous blood from healthy volunteers. However, while the median change is significant, there were RBCs of greater storage time with RP values that were found to be similar to, or less than that of the median RP of groups of RBCs with less storage time. Therefore, absolute RP values cannot necessarily be presumed based on storage time alone.

4 | DISCUSSION

Given the delicate redox balance that must be maintained in biologic systems, alterations in blood RP may directly affect the overall health and viability of banked blood, contributing to storage lesions due to increases in overall oxidative stress,[13] potentiation of red cell lysis in oxidized states,[14] impacts on clot formation and contraction,[15] and decreases in red cell deformability that can be present in states of increased oxidative stress.[16] As a result, these alterations can contribute direct effects on systemic coagulopathy, as well as impairments in the ability of red cells to traverse the microcirculation and provide effective systemic oxygen delivery, yet there are currently few, if any, means by which to make these measurements in the clinical setting, and none by which to make them at the bedside where these measurements could make the most impact. However, we can now make direct POC measurements of RP that could provide new insight into overall oxidative stress, and the degree of oxidative injury present in RBCs and in circulating blood, as the RP measured reflects the overall (ambient) redox balance arising from the sum of metabolically active oxidant and reductant species contributing to the signal.

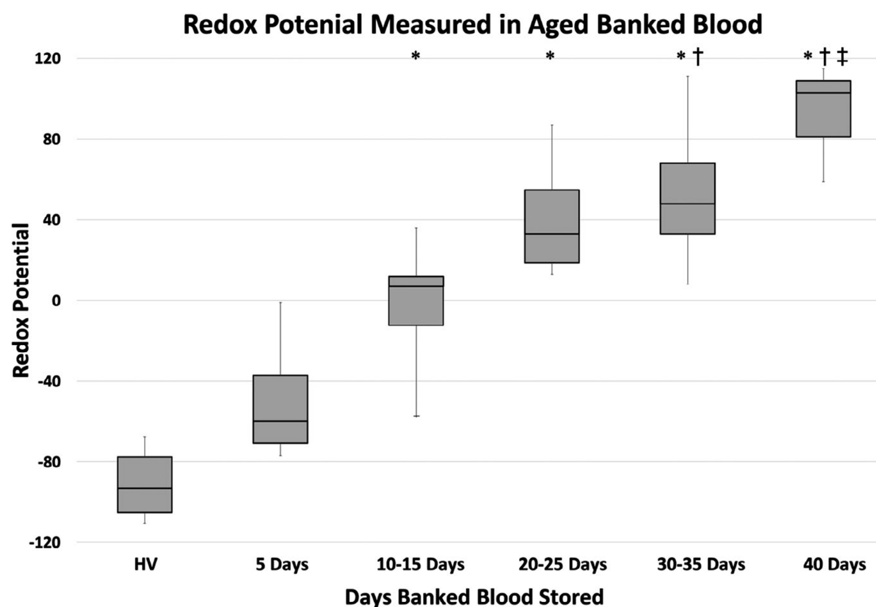

FIGURE 1 Redox potential (RP) measured from multiple random units of red blood cells (RBCs), ranging in age from 5 days to 40 days of age ($n = 32$ total), along with RP measures of peripheral venous blood taken from 10 healthy volunteers (HV). Aged RBC samples were placed into one of five groups depending on duration of storage: 5 days, 10–15 days, 20–25 days, 30–35 days, and 40 days. RP becomes progressively more positive (more oxidized state) over time, with 5-day-old RBCs having an RP closest to that of the peripheral blood of healthy volunteers. *Significant Difference from Day 5 RBCs. †Significant Difference from Day 10–15 RBCs. ‡Significant Difference from Day 20–25 RBCs. Mann–Whitney *U* test with Holm Sequential Bonferroni Adjustment

The more positive the RP, the more oxidized the sample, and the more negative the RP, the more reduced (anti-oxidized) the sample.

There are very few studies of RP in stored RBCs and/or banked blood. While a previous study of RP in stored RBCs did show an increase in oxidation during storage, a small number of RBC units were tested and only those from day 1 and day 42 were included, with no evaluation of RBCs between these extremes of age.[17] In addition, RP was only measured in the supernatant, which may not provide the best measurement for assessing RBCs as a whole, as we have noted dampened/altered RP signals measured from plasma versus whole blood samples taken simultaneously from the same blood draw in previous studies.[11] Further, our colleagues at VCU also noted that RP becomes more positive over time of storage through studying single RBC units over 56 days, but they evaluated a relatively small number (5 total), and also treated these RBCs with additives to compare the changes in RP among the treated RBC units over time, sampling at day 7, 21, 42, and 56, testing at dates longer than most clinical settings will store RBC units and with few testing time points overall throughout the evaluation period.

While these small studies suggest increasing oxidation may occur over time in stored RBCs, additional studies indicate that administration of older blood units, as much as 14 days and older, can increase both the risk of transfusion related lung injury[18] and the risk of adverse clinical outcomes and mortality in critically ill patients, especially if multiple RBC transfusions are required.[19,20] These effects are attributed to storage lesions that accumulate over time as RBCs are stored, with multiple reports describing increased oxidative injury and changes in redox balance as a major contributing factor in storage lesions.[2-4] Our data support these concepts, demonstrating that overall RP among RBCs tested increases over time, reflecting an increase in oxidation present, and thus oxidative stress, as they age. When compared to the circulating RP of healthy volunteers (representing fresh blood from healthy donors), all RBCs tested were found to have a median RP that was more positive (more oxidated), even when compared to RBCs on day 5 of storage. While time of storage appears to contribute, the discrepancy between healthy volunteers and day 5 of storage may also be related to the way in which the RBCs are processed and stored, producing a more oxidized environment from the onset of collection and processing. Variables contributing to this include temperature and pH variations, as well as the anticoagulant utilized in collection, and could result in an increase in the initial level of oxidation present at the onset of RBC storage.[21]

However, age alone does not accurately predict the RP of individual RBCs as noted above, given some RBCs are less oxidized than both the RBCs of similar storage age and those that have been stored less time than that particular unit. This could be due to multiple factors, but may relate to significant variations in the RP status of any given donor due to multiple variables including age, state of health, comorbid conditions, genetic factors, and medications the subject may be taking at the time of donation. Indeed, significant variations between donors have been recognized for some time, as Dern et al.[22] noted in 1966 that factors such as cell hemolysis vary significantly from one donor to another, and these factors are also consistently different within some donor groups and those related to them. These observations are consistent with our study, as we noted blood RP values among healthy volunteers were quite variable, indicating varying degrees of baseline blood oxidation likely exists throughout the population. This may have implications for donor screening by allowing for better characterization of RBCs throughout initial processing and storage via RP utilization.

Questions also still remain whether there are critical aspects of RBC storage lesions that can adversely impact clinical outcomes for specific patients. A recent trauma study analyzing data from the Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial reported an increased likelihood of 24-h mortality in patients receiving massive transfusions (>10 units) of RBCs if older than 22 days,[23] with a second analysis of PROPPR data finding that a higher, more positive SBI (Scalar Age of Blood Index, indicating older RBC units were used) was associated with both 24-h and 30-day mortality, despite adjustments for total units received and clinical covariates.[24] Traumatic injury itself can produce negative effects on the health and viability of circulating blood by the induction of platelet activation that can stimulate the production of ROS, altering the systemic redox state and ultimately leading to dysregulation of the coagulation cascade.[25] Given that 33% of patients suffering from trauma and hemorrhage present with coagulopathy on admission,[26] if the RP of banked RBCs given to these patients is also altered, the negative effects of storage lesions could be amplified, worsening systemic oxidation and oxidative stress. While our study is performed entirely in vitro via segments, with the exception of in vivo measurements from healthy volunteers, we have no data regarding the effect of transfusing RBCs with higher RP values in the clinical setting, yet this study is needed and is forthcoming.

The ability to determine the RP status of RBCs in the blood bank could essentially provide a useful POC blood "vital sign" to evaluate the health and oxidative state of RBCs. With a direct measure of the oxidative stress of any given RBCs planned for transfusion, therapeutic interventions could be delivered to improve the RP, such as antioxidant therapies (e.g., Vitamin C, N-acetylcysteine, others) that have been shown to reduce oxidative stress in RBCs,[5,6] reduce cell damage by free radicals,[27] and preserve red cell energy and overall RBC quality.[7] Although evaluating a limited number of RBC units over time, the VCU group reported evidence that the addition of vitamin C may help stabilize RP over the duration of RBC storage given the progressive oxidation that occurs,[28] and one study of 15 donors noted less decline in antioxidant capacity in blood taken from the same donors after receiving a 10-day regimen of antioxidant supplementation versus blood collected from them prior to initiating the antioxidant regimen.[27] In this context RP measures could be used as a gauge for providing *systemic* antioxidant therapy as well, such as those cases in which a patient's RP value increases significantly (increased oxidation) after acute resuscitation with RBCs. In the end, having bedside POC measurements of RP could add a new dimension to patient monitoring that could improve both banked blood viability, its effectiveness when given to those in need of transfusion, and the overall health and function of circulating blood in these patients.

There are a number of important limitations to this study. Overall, the total number of units sampled was relatively small. Sampling was done from the RBC segments and not directly from the blood bag itself where RP may have been different, as there could be segment properties that cause variations in RP compared to the main RBC unit (e.g., hemoglobin concentration and/or degree of hemolysis present and difference in plastic storage material). Although we did not evaluate this variable in this study, current studies are underway that include direct sampling from the RBC unit bag itself. We also only performed single RP measures on each sample, however our previous work has demonstrated excellent reproducibility of measurement.[10,11] Given this and the small sample size of the segments we did not feel it necessary to perform duplicate measures. We did not measure RP of RBCs at day 0, although they were not available due to the time required for processing and subsequent delivery to the blood bank after initial collection from blood donors. While we did measure RP in fresh whole blood of healthy volunteers, this blood was not processed in the same way that occurs with blood donation. As mentioned earlier, such processing could change RP, and we decided to make direct measures of RP from healthy volunteers as the result would more likely reflect circulating RP values of donors and patients receiving transfusions. Finally, we made no additional measures of oxidative stress or RBC damage such as fragility-deformability or oxygen carrying capacity (p50). Thus, it is not possible to know with certainly the extent of storage lesions present at RP values measured in this study, and given that we did not study RP measurements over time in a single RBC unit, we cannot state definitively whether a given RP value will be predictive of future RP in a given RBC unit.

5 | CONCLUSIONS

There are significant differences in RP between freshly stored RBCs and all others, with RP becoming more positive over time. However, storage time alone does not predict RP, indicating RP screening may be important independent of age and may serve as a marker of RBC health. Targeting RP may enable the use of antioxidant therapies to restore RP balance in stored RBCs, as well as systemically in those receiving multiple transfusions, improving the clinical effectiveness of RBCs and potentially reducing associated morbidities.

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CONFLICT OF INTEREST

Authors Daniels, Collinson, and Ward hold a patent for the nanoporous gold electrodes used in this study; however, they receive no financial benefits or incentives from this work. The authors have no other conflicts to disclose.

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