Estimation of Achievable Oxygen Consumption Following Transfusion With Rejuvenated Red Blood Cells

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Erythrocyte storage induces a nonphysiological increase in hemoglobin-oxygen affinity (quantified by low p50, the oxygen tension at 50% hemoglobin saturation), which can be restored through biochemical rejuvenation. The objective was to mathematically model the impact of transfusing up to 3 standard allogeneic units or rejuvenated units on oxygen delivery (DO_2) and oxygen consumption (VO_2). Oxygen dissociation curves were generated from additive solution-1 red blood cell (RBC) leukoreduced units (n = 7) before and after rejuvenation following manufacturer's instructions. Two of these units were used to prepare standard or rejuvenated donor RBC and added to samples of fresh whole blood. These admixtures were used to construct an in vitro transfusion model of postoperative anemia and determine a linear equation for calculating the sample p50, which was subsequently used to calculate DO_2 and VO_2 after simulated transfusions. Whole blood-packed red blood cell unit admixture p50s could be predicted from a linear model including the p50 of its components, the mass fraction of the transfused component, and interaction terms ($R^2 = .99$, $P < 0.001$). Transfusion with standard units slightly, but significantly, increased projected DO_2 compared with rejuvenated units ($P = 0.03$), but rejuvenated units markedly increased projected VO_2 ($P = 0.03$). Standard units did not significantly change VO_2 relative to pre-transfusion levels ($P > 0.1$). Using high-p50, rejuvenated RBC in simulated transfusions greatly improved projected VO_2, indicating the potential for increased end-organ oxygen availability compared with standard transfusion. Patient capacity to increase cardiac output after cardiac surgery may be limited. Transfusing high-p50 RBC in this setting may improve the perioperative care of these patients.

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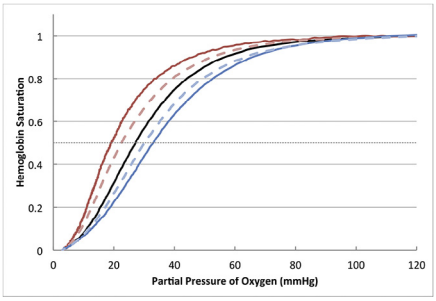

Oxygen dissociation curves for standard (red) and rejuvenated (blue) RBC units.

Central Message

Systemic hemoglobin oxygen affinity changes predictably with sequential transfusions of RBCs. Use of RBCs modified to have low oxygen affinity is likely to increase end-organ oxygen availability.

Perspective Statement

Cardiac surgical patients frequently have limited capacity to increase their cardiac output to compensate for postoperative metabolic demand. Modulation of hemoglobin oxygen affinity is a largely unexplored means of increasing end-organ oxygenation in patients with low cardiac reserve. Our mathematical model predicts increases in end-organ oxygenation with use of low-affinity RBC transfusion.

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INTRODUCTION

Red blood cell (RBC) transfusion is a common intervention in cardiac surgery, with approximately half of all patients requiring more than 1 RBC unit in the perioperative setting.[1] Loss of RBC mass in the form of hemorrhage impairs end-organ perfusion, leading to renal,[2] liver,[3] and bowel[4] injury. Ultimately, the goal of RBC transfusion in this population is to support hemodynamic stability after blood loss and prevent end-organ dysfunction, which is strongly linked with short-term mortality.[5] The hemodynamic improvement after RBC transfusion is particularly important, as the increased myocardial demand induced by homeostatic compensation for hypoperfusion can prove deleterious in patients with low cardiac reserve. RBC transfusions are generally effective in increasing blood oxygen delivery, and this has been shown to mitigate compensatory increases in cardiac output.[6]

The hazards of transfusion are well known, particularly in cardiac surgery where perioperative transfusion has been associated with increases in short-term and remote mortality.[7,8] Further explorations of these associations have also shown a degree of dose dependence, in that patients undergoing fewer transfusions have better outcomes,[9,10] although a recent large randomized controlled trial found that restrictive transfusion protocols do not have a demonstrated mortality benefit compared with liberal strategies.[11] Although it has not been conclusively determined whether the demonstrated associations are causal or caused by the confounding variables of poorer overall health status in transfused patients, many institutions have opted to develop transfusion protocols and preoperative optimization to minimize patient exposure to blood products.

A major aspect of the so-called RBC storage lesion is depletion of 2,3-diphosphoglycerate (2,3-DPG), resulting in a pronounced increase in hemoglobin oxygen binding affinity (corresponding to a decrease in p50, the partial pressure of oxygen at which hemoglobin is 50% saturated).[12] Furthermore, significant decline in p50 occurs within the first 7 days of storage,[13] which may help to explain the negative findings of the RECESS trial, which sought to find a mortality difference between cardiac surgery patients receiving fresher and those receiving older RBC units.[14] As the average age of transfused RBC units ranges between 19 and 25 days depending on institution,[15] the majority of RBCs transfused have low p50. High-affinity RBCs bind oxygen avidly in alveolar capillaries, but do not release oxygen at end-organ tissues as effectively as RBCs with physiological, or lower, oxygen affinity.[16] One avenue for minimizing transfusion burden in this patient population is to modulate the oxygen binding affinity (p50) of hemoglobin in transfused blood. Could 1 unit of low oxygen affinity blood offer the benefits of 2 units of standard blood?

Modulation of p50 can be achieved through the process of RBC rejuvenation, which replenishes biochemical intermediates that allow for the increased production of 2,3-DPG.[17] Elevated p50 allows for increased peripheral oxygen offloading, which has been shown to increase the oxygen consumption (VO_2) in cardiac surgery patients.[18] In this paper, we mathematically model changes in hemodynamic and oxygenation parameters in an in vitro simulation of postoperative anemia and sequential transfusion of blood with low p50 (standard packed red blood cell units [PRBCs]) or high p50 (rejuvenated RBCs), with the intent to quantify the hemodynamic consequences of p50 modulation in patients with limited cardiac reserve. If a patient's baseline end-organ homeostasis requires a specific systemic level of oxygen consumption (VO_2), then this same patient in the setting of postoperative anemia will require a compensatory increase in cardiac output to maintain the required levels of oxygen consumption necessary for proper end-organ function. To explore the potential for clinical benefit in transfusing rejuvenated RBCs in the setting of cardiac surgery, we will test the hypothesis that rejuvenated RBC transfusions significantly increase the achievable VO_2 in a model compared with standard PRBC transfusions.

METHODS

Preparation of Rejuvenated RBC Units

Leukoreduced 21-day-old donor PRBC units (n = 7) stored in AS-1 were acquired from local blood banks. Rejuvenation was performed using rejuvesol Red Blood Cell Processing Solution (Citra Labs, Braintree, MA) according to manufacturer's instructions. Briefly, rejuvenation solution was added to RBC units using sterile technique and units were then incubated for 1 hour at 37°C in a Plasmatherm blood warmer (Barkey GmBH, Leopoldshoehe, Germany). After 1:4 dilution in 0.9% saline, units were washed with a Continuous Autotransfusion System (C.A.T.S.; Fresenius Kabi AG, Bad Homburg, Germany) using the High Quality Wash setting, as previously described.[19]

Oxygen Affinity Measurement

Oxygen affinity of each sample was measured by automated tonometry using a Clark oxygen electrode (Hemox Analyzer, TCS Scientific, New Hope, PA), according to manufacturer's instructions. Whole blood or PRBC (50 μL) was mixed with 5 mL of Hemox Buffer, 20 μL of 25% bovine serum albumin, and 10 μL of antifoaming agent. The mixture was introduced into the cuvette of the Hemox Analyzer and was exposed to variation in oxygen tension, whereas changes in oxyhemoglobin were measured by dual-wavelength spectrophotometry at 560 nm and 570 nm. This procedure generated an oxygen dissociation curve (ODC) from which the p50 and Hill coefficient were derived.[20]

Modeling of p50 Changes in Blood Admixtures

Because the 50% saturation point of a blood admixture will lie on the linear portion of the Hill plot, we began by using the Hill equation[21] to derive the p50 of an equal-parts admixture. We have assumed that the saturations of the 2 components will be additive, and thus s_1 and s_2 denote the component saturations of samples 1 and 2 at the final oxygen tension p_f. The p50 values of samples 1 and 2 are denoted p_1 and p_2, respectively. The Hill coefficient, n, represents the degree of hemoglobin cooperative binding and varies with the shape of the classic oxygen dissociation curve. The equations in (1) are derived from the Hill equation, and equation (2) follows from the fact that overall admixture saturation must be 50% at p_f.