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Patients with sickle cell anemia on simple chronic transfusion protocol show gender differences for hemodynamic and hematologic responses to transfusion

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Abstract

Background—Chronic transfusion therapy (CTT) is a mainstay for stroke prophylaxis in sickle cell anemia, but its effects on hemodynamics are poorly characterized. Transfusion improves oxygen carrying capacity, reducing demands for high cardiac output, while decreasing hemoglobin S%, reticulocyte count, and hemolysis. We hypothesized that transfusion would improve oxygen carrying capacity, but that would be counteracted by a decrease in cardiac output due to increased hematocrit and vascular resistance, leaving oxygen delivery unchanged.

Study Design and Methods—To test this hypothesis, we examined patients on CTT immediately pre transfusion and again 12–120 hours post transfusion, using echocardiography and near infrared spectroscopy.

Results—Comparable increases in hemoglobin and hematocrit, and decreases in reticulocyte count and hemoglobin S with transfusion were observed in all patients; but males had a larger rebound of hemoglobin S%, reticulocyte count, and free hemoglobin levels between transfusions. In males, transfusion decreased heart rate by 12%, stroke volume by 15%, and cardiac index by 24% while estimates for pulmonary and systemic vascular resistance rose, culminating in 6% decrease in oxygen delivery. In contrast, stroke volume and cardiac index, systemic and pulmonary vascular resistance did not change in women following transfusion, such that oxygen delivery improved 17%.

Conclusion—In our sample population, males exhibit a paradoxical reduction in oxygen delivery in response to transfusion because the rise in vascular resistance is larger than the increase in oxygen capacity. This may result from an inability to adequately suppress their hemoglobin S% between transfusion cycles.

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Keywords

Pulmonary Circulation; Vascular Resistance; Cardiopulmonary Interactions; Cardiovascular Performance

Introduction

Sickle cell anemia (SCA) is a common hemoglobinopathy that causes significant morbidity and mortality.[1] Cardiac output is increased in non-transfused SCA subjects, proportional to their anemia, preserving their tissue oxygen delivery.[2–5] Also, vascular disease is a common cause of morbidity in SCA and its etiology is multifactorial with contributions from chronic intravascular hemolysis, via release of plasma free hemoglobin, as well as vascular inflammation and abnormal blood rheology.[6,7] LDH, plasma free hemoglobin and arginine:ornithine ratio have been described elsewhere as markers of intravascular hemolysis.[8] Chronic transfusion therapy reduces complications of sickle cell disease and (CTT) is utilized as secondary prevention for SCA patients following stroke, as primary prevention in children at high risk for stroke based on transcranial Doppler (TCD), or in patients having intractable sickle crises.[9–15] CTT decreases hemoglobin S concentration and increases oxygen carrying capacity, which intuitively ought to improve both chronic intravascular hemolysis and red cell deformability, thereby improving tissue oxygen delivery.[16,17] However, increased hematocrit acutely following a single transfusion increases whole blood viscosity and vascular resistance in a nonlinear manner.[18–20] Cardiac index may therefore fall in response to increased hematocrit, partially or completely counteracting the increase in oxygen carrying capacity. In fact, the acute hemodynamic consequences of transfusion therapy and their overall affect on tissue oxygen delivery are poorly characterized and unpredictable.[21] In this study we evaluate the acute effects of transfusion on hemodynamics and oxygen delivery in 25 SCD patients on chronic transfusion therapy. We hypothesized that despite decreasing hemoglobin S% and increasing hemoglobin/hematocrit, transfusion would produce balanced effects on cardiac index and oxygen capacity leaving tissue oxygen delivery unchanged.

Patients and Methods

Patients

This study was a prospective, cross sectional evaluation of the acute hemodynamic effects of transfusion in 26 chronically transfused SCD patients. One patient was excluded due to lack of post transfusion data. Subjects with HbSS Sickle Cell Anemia on chronic transfusion protocol were identified in the outpatient transfusion clinic at Children's Hospital Los Angeles or by their primary hematologist and were enrolled between August 2008 and September 2010. The exclusion criteria were age <10 years old, chronic transfusion therapy <1 year, sickle crisis within the previous four weeks, defined as requiring inpatient admission or an emergency room visit with an increase in pain medications above their baseline usage for greater than 2 days. All patients provided written informed consent or parental consent and patient assent were obtained according to the protocol approved by the Committee for Clinical Investigation at Children's Hospital Los Angeles.

Most patients receive simple transfusions every three weeks. All units are extended crossmatched (C, E, Kell) packed RBC less than 14 days old, unless there is no antigen matched unit available in that age range. Transfusion frequency and volume are modified to maintain HgB S% less than 30% and immediate post transfusion Hb < 12 g/dl to minimize hyperviscosity. If patients have adequate venous access, erythrocytophersis is utilized, but in our cohort only three patients undergo regular erthrocytophoresis. Aliquots of blood are all

stored in CPDA. All patients underwent history & physical exam, echocardiography, and laboratory analysis on the morning of transfusion prior to receiving any blood products. The experimental protocol was subsequently repeated 12 – 120 hours post transfusion (mean 2.3 days, SD=1.4 days) when peritransfusional changes in fluid, hormonal, and immune axes should have dissipated and post transfusional hematocrit stabilized.

Echocardiography

One investigator (J.D.) performed an echocardiogram, using a Philips IE 33 ultrasound machine, version 3.0.2.711 prior to and following transfusion. Standard 2D, M-mode and tissue Doppler derived function measurements were made according to published standards.[22–24] Cardiac output measurements were made utilizing pulsed wave Doppler velocity time-integral (VTI) measurements at the level of the left ventricular outflow tract; cardiac output was converted to cardiac index by normalizing to body surface area. Systemic vascular resistance index (SVRi) was calculated using cuff derived mean arterial blood pressure, inferior vena cava (IVC) collapse estimate of right atrial pressure, and cardiac index.[25] Pulmonary vascular resistance index (PVRi) measurements were performed as described in Dahiya et. Al., using mitral E/E′, tricuspid regurgitation (TR) jet velocity derived pressure estimate and cardiac index.[26] M-mode shortening fraction and ejection fraction by Simpson's method were used as objective measures of global systolic function. Oxygen delivery was measured using the product of cardiac index * oxygen content (hemoglobin x 1.34 mlO2/g x resting oxygen saturation), neglecting the insignificant contribution of dissolved oxygen.

Near Infrared Spectroscopy

Near infrared spectroscopy (NIRS) measures oxyhemoglobin saturation, providing an estimate of regional mixed venous oxygen saturation. This has been correlated with both tissue oxygen consumption and regional flow.[27] Measurements were made with a NIRS device (Somanetics Inc Troy, MI). Sensors were placed on the dorsal surface of both hands at rest, prior to and following transfusions. Samples are acquired every 4 seconds over 3–5 minutes and averaged.

Hematologic Analysis

A venous blood sample of ~15cc was drawn prior to transfusion and at the post transfusion study visit to evaluate hematocrit, hemoglobin, white blood cell count (WBC) and platelets. Markers of hemolysis were measured, including LDH, plasma free hemoglobin and arginine ornithine ratio. High sensitivity CRP (hsCRP) was measured as a marker of inflammation. Iron indices were also measured.

Data Analysis

Cardiovascular and hematologic responses to transfusion were evaluated by two-sided, paired T-tests. Wilcoxon Rank Sum Test was used when data were not normally distributed. Linear regression was performed for correlations of continuous data. JMP (version 5.1.2, SAS Institute Inc., Cary, North Carolina) was used for all statistical analyses.

Results

Demographics

25 patients with sickle cell anemia on chronic transfusion therapy, 13 female (52%) and 12 male (48%), were enrolled and had complete data. Demographics are shown in Table 1. Males tended to be taller than females; but both sexes were well balanced for age, weight, body mass index and body surface area. Males and females had similar duration of CTT and

indices of iron overload, although liver iron trended higher in females. There was no sex difference in the frequency or volume of transfusions over the previous year nor was there a difference in the age of the blood or volume of blood given on the day of the study. Males were studied an average of 25.1 days (range 13–41) since their prior transfusion compared with 22.2 days (range 14–41) for the females but this difference did not reach statistical significance. There were two allo-immunized males and two auto-immunized males. Zero females were allo-immunized and one female was auto-immunized. One male with an anti-E antibody had increased plasma free hemoglobin (50 mg/dl) and an elevated TR jet >2.5m/s. Another male with both cold and warm autoantibodies also exhibited increased plasma free hemoglobin (35 mg/dl) and a TR jet >2.5m/s. Males and females had similar reasons for starting chronic transfusion therapy with an even distribution among stroke/CVA (9 patients), elevated trans-cranial Doppler (9 patients), recurrent acute chest episodes (6 patients) and pulmonary hypertension (PH) diagnosed by right heart catheterization (1 female patient). CTT normalized the TR velocity and right heart pressures prior to participation in this analysis. Three of these patients were started on CTT with a history of elevated TR jet >2.5m/s, including the female patient who was diagnosed with PH.

Average Laboratory and Hemodynamic Measurements

Table 2 compares hematologic and hemodynamic variables for males and females for the pre and post transfusion visits. Laboratory indices of iron were only measured pre-transfusion.

Hemoglobin and hematocrit were similar in males and females; however, males had increased %HbS, reticulocyte count, platelet count, and plasma free hemoglobin. Figure 1 demonstrates %HbS and reticulocyte count rise sharply with time following last transfusion in males but not females. Plasma free hemoglobin also appears to rise faster in the males, however, this difference did not reach statistical significance. Although platelets are increased in males, platelet count did not vary with transfusion interval. High sensitivity CRP and LDH were significantly elevated compared to reference values for both males and females.

Measures of diastolic function, E/A and E/E′, were normal; however, females tended to have higher LV E/E′ ratio at both the LV septal and lateral wall, suggesting slightly higher end diastolic pressure. The common objective echocardiographic measures of systolic function, ejection fraction and shortening fraction, were within normal limits and similar for male and female patients. LV and RV myocardial performance indices (MPI), were significantly elevated compared to published normal values (0.38 +/−0.06 for the LV and 0.37 +/−0.05 for the RV), but there were no sex differences.

Heart rate was higher in females despite similar hemoglobin and hematocrit and there was a trend toward higher cardiac index. Systolic, diastolic, and mean arterial blood pressure was similar between male and female patients. TR jet and pulmonary vascular resistance estimates were significantly increased in males but there was no difference in the average systemic vascular resistance or oxygen delivery. There was no association between plasma free hemoglobin and pre-transfusion cardiac index, SVRi or O2 delivery in the male and female patients. For the group, there was a strong association between pre transfusion plasma free hemoglobin and pre transfusion TR jet velocity (R^2=0.43, P=0.002).

Age of the blood, frequency of transfusions over the previous year, volume of blood over the previous year and the number of years on transfusion (Table 1) are not associated with the pre or post-transfusion reticulocyte count, hemoglobin S% and plasma free hemoglobin by linear regression (data not shown). There is no association between blood age, previous year

blood volumes or years on transfusion and TR jet, cardiac index, oxygen delivery, and SVRi (data not shown),

Pre to Post Transfusion Changes in Hemolysis, Inflammation, Cardiac Function and Hemodynamics

Changes in laboratory markers, vital signs, echocardiography and NIRS values in response to a single transfusion episode are demonstrated in Table 3; values displayed are for male, female and pooled responses. Hemoglobin, hematocrit, hemoglobin S% and reticulocyte count responded intuitively to transfusion in both sexes. Regardless of sex, plasma free hemoglobin decreased with transfusion if the pre-transfusion level was greater than 20mg/dL (Figure 2).

Systolic and diastolic markers of cardiac function were minimally affected by transfusion in either sex. Mitral E to A ratio increased, consistent with a change in preload. Shortening and ejection fractions remained the same and there were no significant changes in RV or LV MPI.

Transfusion reduced cardiac index by 15% (0.5 L/min/m^2) and lowered heart rate, commensurate with the increase in hemoglobin. Males had a disproportionate reduction in cardiac index (Table 3, Figure 3), thereby decreasing oxygen delivery despite the improvement in oxygen carrying capacity with transfusion. While transfusion increased oxygen delivery 17% in women, it reduced oxygen delivery in males by 6%. NIRS recordings from the hands parallel these observations, with peripheral venous oxygen saturation improving with transfusions only in females following transfusion.

Reduced cardiac index in males following transfusion was predominantly secondary to reduction in stroke volume index; heart rate fell an average of 9 beats per minute in both sexes. Systolic, diastolic and mean arterial blood pressure did not change with transfusion. Systemic and pulmonary vascular resistance indices increased 25% and 15% respectively, reaching significance only in males. Paradoxical to the group increase in PVRi after transfusion, the prevalence of TR jet > 2.5 m/s decreased following transfusion (Figure 4).

Discussion

Sickle cell anemia has known cardiovascular complications including stroke, pulmonary hypertension, chronic leg ulcers, heart failure and sudden death. The etiology is multifactorial, resulting from chronic hemolysis and decreased nitric oxide bioavailability, inflammation, abnormal blood viscosity from reversible and irreversible sickling, and chronic large vessel and microvascular dysfunction.[28–30] Chronic transfusion therapy is used to decrease the incidence of first time and recurrent stroke in patients with sickle cell anemia, however, its effects on other vascular complications is poorly characterized.[12,15,31] Furthermore, the mechanism by which CTT decreases the risk of stroke is not well understood. It is thought that suppression of endogenous erythrocyte production and circulating hemoglobin S% is essential.[17] Our initial hypothesis centered on hemodynamic changes in a population of SCA patients on chronic transfusion therapy. We found that our study population did not significantly increase oxygen delivery after a single transfusion; however, there was wide interpatient variability. When we examined age and sex differences for transfusion-induced changes in oxygen delivery, there were marked sex differences in both hemodynamic measures as well as hemoglobin S%, plasma free hemoglobin, reticulocyte count and platelet count. Despite the post hoc nature of the sex differences, we cannot ignore them. Males demonstrated sharp increases in reticulocyte count, hemoglobin S % and plasma free hemoglobin between transfusions, compared to females. This was not related to timing between the previous transfusion and the first study visit, nor was it related

to total volume or frequency of transfusions over the previous year. This difference in hemoglobin S% might represent one mechanism to explain increased vascular complications previously observed in males with SCA[1,32], and may contribute to the higher systemic vascular resistance, TR velocity and pulmonary vascular resistance estimates documented in our study. Testosterone directly stimulates marrow activity and could also be responsible for the sex disparity but we did not have sufficient sample size or pre-pubertal males to test this hypothesis.[33]

Transfusion had surprisingly complicated effects on hemodynamics that were also sex specific. Overall, transfusion decreased cardiac output by reducing heart rate and stroke volume, as expected. Males demonstrated a more pronounced increase in total systemic resistance and estimated pulmonary resistance with significant decreases in stroke volume and cardiac index. Much to our surprise, oxygen delivery decreased in males following transfusion, while it increased in females. In this cohort, we cannot determine whether the resistance difference and resultant oxygen delivery difference seen in the males is due to a primary decrease in stroke volume or a primary increase in vascular resistance. The former would require isolated impairment of cardiac mechanical properties, not detectable by echocardiography, which is unlikely. Alternatively, changes in vascular resistance could be secondary to abnormal rheology from an increased platelet count, hemoglobin S% and reticulocyte count or from NO scavenging by plasma free hemoglobin. NO, viscosity and cellular deformability modulate vascular resistance at multiple levels, but the microvasculature is particularly sensitive to increased viscosity and red cell deformability, which is directly related to hemoglobin S.

Our estimate of PVRi is a combination of TR Jet (estimate of PA pressure), E/E′ (correlate of pulmonary capillary wedge pressure) and CI. In our cohort, the PVRi difference was due to a higher TR jet and lower E/E′ in the males, suggesting pre-capillary increases in PA pressure; right heart cath would be required to prove this hypothesis. Males have a propensity for more severe vascular disease[6,32] and the vascular response to transfusion could be modulated by sex differences in marrow suppression. Plasma free hemoglobin levels correlated with TR jet, although the relationship was primarily driven by the higher TR in males. Plasma free hemoglobin also correlated with PVRI, but the effect was much weaker (r^2=0.09, p=0.015). We could not demonstrate an effect of hemoglobin S%, reticulocyte count or LDH on TR jet, SVRi, CI or O2 delivery in either sex. However, given the diffuse endotheliopathy in sickle cell disease, global hemodynamics are unlikely to be sensitive enough to detect microcirculatory disease, where hemoglobin S would exert most of its effects.

Global measurements of oxygen delivery only reflect potential oxygen supply to organs; effective tissue oxygen delivery requires an intact microvascular bed, which is often compromised in SCD. However, near infrared spectroscopy tracks a weighted combination of tissue oxygenated and deoxygenated hemoglobin at the microvascular level and is a robust metric of tissue oxygen supply-demand balance[38,39]. Changes in local tissue oxygenation by NIRS mirrored the sex differences observed in global oxygen delivery. Greater microvascular disease and lower average NIRS saturation would not be surprising, given that higher plasma free hemoglobin, platelet count, hemoglobin S% and reticulocyte count have all been implicated in chronic microvascular disease in SCA patients.[28,30,40]

Multiple studies have shown that basic metrics of cardiac systolic performance are preserved in patients with sickle anemia.[2,3] MPI, which includes both isovolumic contraction (IVCT) and relaxation times (IVRT) and ejection time (ET), takes into account both diastolic and systolic function. This was significantly elevated relative to population norms, signifying poor myocardial performance similar to patients with dilated cardiomyopathy, primary

pulmonary hypertension and other systemic diseases.[41–45] This metric although abnormal, demonstrated no sex differences and little change with transfusion, suggesting a ubiquitous maladaptation present in these patients. The mechanism of decreased myocardial performance is unclear, whether it is primarily a change in IVRT, IVCT or ET cannot be answered in our study.

E/E′ has been shown to correlate with pulmonary capillary wedge pressure (PCWP) and LV end diastolic pressure (LVEDP).[23] Both the RV and LV E/E′ were within normal limits for published norms, however the females had a higher E/E′ both pre and post transfusion suggesting a higher PCWP/LVEDP as a chronic response to anemia. Interestingly an increase in MV E/A was seen in our patients and this was due to a 10% (P=0.08) and 12% (P=0.009) decrease in mitral A wave velocity for the males and females respectively. This is consistent with previous studies showing decreased LV compliance and increased incidence of diastolic heart failure in females.[46,47] With the exception of MPI, systolic and diastolic function parameters were within normal limits of published norms, demonstrating that SCA patients on CTT are able to compensate for increased cardiac output. Importantly, the disparate effect of transfusion on oxygen delivery does not appear to result from changes in cardiac systolic or diastolic function but rather hematologic and peripheral vascular effects.

Our study was limited by its small size and cross-sectional nature, we acknowledge the need for similar studies in a larger cohort of patients. In addition, we would like to assess these patients longitudinally to determine if these changes are stable over time and whether adjusting transfusion parameters or stricter transfusion protocols would alter the hemodynamic and hematologic irregularities. There was no transfusion control group because non-transfused SCA patients only receive a transfusion during severe crisis events such as acute chest syndrome and our goal was study sickle cell patients during a steady state period. In order to understand how patients on CTT differ, at a baseline, from non-transfused patients and healthy controls, the changes that surround a single transfusion must be understood. Healthy individuals do not receive blood transfusions, making healthy control experiments unrealistic; therefore, our observations are limited to pre and post transfusion measurements using each patient as their own control. We then utilized paired statistics to help increase the power of our study. There is also inherent selection bias when studying patients on CTT because their hemorheologic and vascular disease is more severe. Echocardiographic estimation of cardiac output, which underlies some of our hemodynamic measurements, is limited by certain mathematical assumptions. Similarly, noninvasive estimates of systemic and pulmonary vascular resistance have been derived in populations other than sickle cell disease. Paired differences across transfusions and relative sex differences reduce systematic errors from these geometric assumptions but absolute vascular resistances can only be obtained through cardiac catheterization. However, correspondence of our echocardiographic predictions of oxygen delivery with tissue NIRS response is reassuring that our observations are physiologically relevant.

In conclusion, each transfusion lowers heart rate and cardiac index in patients on CTT. Males demonstrate a disproportionate reduction in cardiac index and stroke volume indices such that oxygen delivery declines following each transfusion. This likely represents more extensive vascular disease as a result of hormonal differences, greater average hemoglobin S concentrations, reticulocyte counts, and cell-free hemoglobin. Thus males may benefit from stricter adherence to 21-day transfusion cycles, utilization of exchange transfusions, or concomitant use of hydroxyurea and CTT. Further work is necessary to determine whether our observed sex differences in vascular function are apparent prior to sexual maturation and hold true for a larger population of SCA patients.

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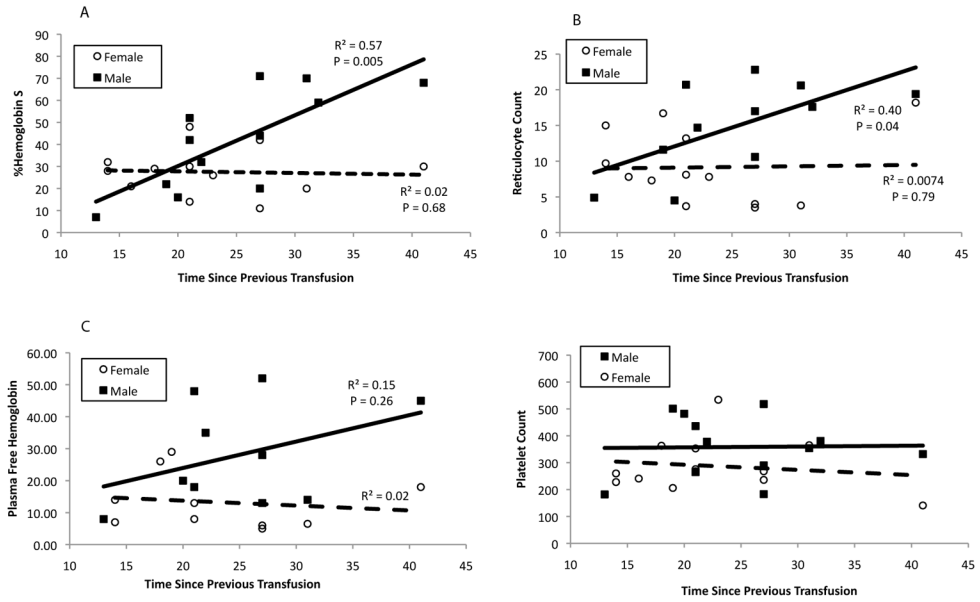

Figure 1. Sex differences in recovery of hemoglobin S% (A), reticulocyte count (B), plasma free hemoglobin (C) and platelet count (D)

Male patients are denoted by the filled squares and a solid regression line and female patients by open circles and a dashed regression line. Pearson correlation coefficient and P value are shown for significant differences. Pre-transfusion values were correlated with the time from previous transfusion to the study visit to determine sex differences in recovery of these variables. Males increased hemoglobin S% and reticulocyte count and tended to increase plasma free hemoglobin levels at a faster rate following transfusion.

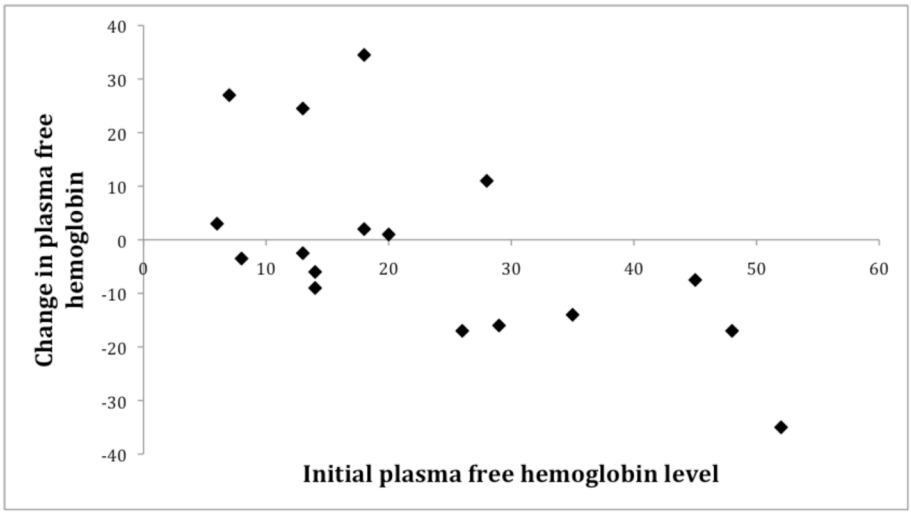

Figure 2. Change in plasma free hemoglobin level after transfusion

Figure suggests that patients with an initial plasma free hemoglobin level >20mg/dL will have a decrease in free hemoglobin with transfusion, however, patients with levels <20mg/dL could have increases or decreases in their level.

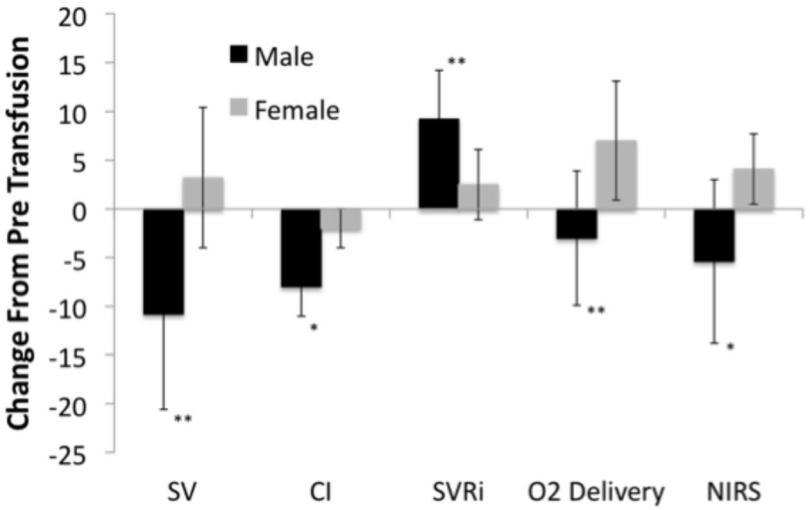

Figure 3. Hemodynamic changes in male and female patients after transfusion

* indicates a trend difference between male and female patients ($0.05 < p < 0.10$), ** indicates a significant difference ($p < 0.05$). SV = stroke volume (ml), CI = cardiac index ($dL/min/m^2$), SVRi = systemic vascular resistance index (woods units), NIRS = near infrared spectroscopy (%). Figure shows that males decreased stroke volume and cardiac index to a greater degree than females. The males also increased systemic and pulmonary vascular resistance to a greater degree. Effects combined to decrease oxygen delivery in males versus increase in females.

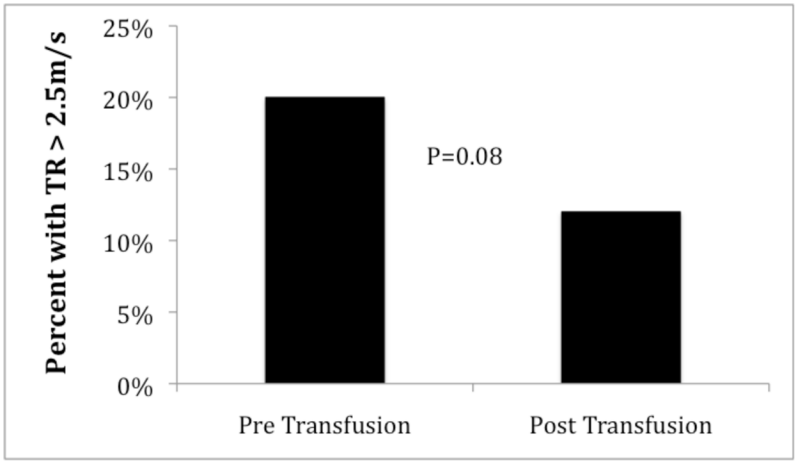

Figure 4. Change in percentage of patients with a TR jet velocity >2.5m/s

Figure demonstrates a small decrease in the incidence of TR jet >2.5m/s after transfusion. No patient with a TR jet <2.5m/s had a TR jet >2.5m/s post transfusion. All patients in our cohort with TR jet >2.5m/s were male, but the percentage values were based on the total population.

Table 1

Demographics, transfusion data, MRI findings, and medication data in patients on chronic transfusion therapy.

Demographics	Male (n=12)	Female (n=13)	P-Value
Age (±SD)	18.2 (±6.2)	21.3 (±10.0)	0.35
% African American	83	85	
Height in cm (±SD)	167.7 (±16.7)	157.2 (±11.5)	0.09
Weight in kg (±SD)	60.4 (±16.9)	56.1 (±14.9)	0.5
BMI kg/m2 (±SD)	21.0 (±3.0)	22.4 (±4.2)	0.35
BSA m2 (±SD)	1.67 (±0.31)	1.56 (±0.25)	0.33
Volume of blood given on the day of transfusion (ml/kg)	8.4 (1.9)	9.5 (3.8)	0.42
Age of blood given on the day of transfusion (days)	22.0 (6.1)	17.8 (9.1)	0.19
Number of Transfusions Over the Previous Year	17.3 (6.0)	17.9 (5.0)	0.79
Volume of Blood Over the Previous Year (ml/kg)	172.0 (113.0)	234.4 (108.9)	0.17
Days Since Last Transfusion (±SD)	25.1 (±7.4)	22.2 (±7.7)	0.36
Years on Transfusion Therapy (±SD)	8.5 (±5.4)	8.0 (±4.3)	0.83
Time Between Study Visits (days)	2.2 (±1.5)	2.4 (±1.4)	0.71
Allo-immunization	2	0	
Auto-immunization	2	1	
Cardiac T2* (ms)	36 (±5.4)	33.6 (±9.3)	0.47
Liver Iron (mg/g)	16.2 (±12.6)	26.1 (±13.1)	0.07
Reason for Transfusions			
CVA	4	5	
Abnormal TCD	5	4	
recurrent Acute Chest	3	3	
Pulmonary Hypertension	0	1	
Hydroxyurea therapy	2	2	
Iron Chelator			
none	1	2	
desferal		1	
ex-jade	11	9	
ex-jade + desferal		1	

Data are expressed as mean ± one standard deviation. BSA = body surface area, BMI = body mass index, CVA = cerebrovascular accident, TCD = transcranial doppler

Table 2

Pre and post transfusion average data for laboratory markers, diastolic function, systolic function and hemodynamics for male and female patients.

Laboratory Value	Male Pre	Female Pre	P-Value	Male Post	Female Post	P-Value
WBC (K/uL)	14.7±4.9	13.3±4.6	0.49	14.8±5.8	12.1±3.5	0.19
Platelet (K/uL)	358.5±114.4	287.6±97.8	0.11	346.7±92.7	260.8±84.0	**0.03**
Hematocrit (%)	28.0±2.2	28.7±2.9	0.49	34.3±3.0	34.1±3.3	0.89
Hemoglobin (g/dL)	9.6±0.7	9.4±1.1	0.64	11.9±0.9	11.6±1.2	0.63
Hemoglobin S (%)	41.9±22.5	27.6±10.5	0.06	37.7±17.8	21.3±6.9	**0.01**
Reticulocyte Count (%)	14.9±6.3	9.1±5.1	**0.02**	11.2±4.5	5.4±3.1	**0.002**
LDH (U/L)	1366±617	1039±430	0.14	1299±609	1039±449	0.26
Transferrin (mg/dL)	170.6 ±37.8	165.4 ±29.2	0.74	NA	NA	NA
Ferritin (ng/ml)	5297.2 ±6615.3	4635.5 ±2979.8	0.75	NA	NA	NA
Iron Level (mcg/dL)	140.3 ±47.7	198.9 ±113.9	0.1	NA	NA	NA
hsCRP (mg/L)	7.6±6.1	4.0±4.8	0.14	2.8±2.2	5.3±5.5	0.16
Arg/Orn	1.2±0.3	1.0±0.4	0.19	1.1±0.5	1.2±0.4	0.55
Plasma Free Hemoglobin (mg/dL)	28.1±16.0	13.3±8.6	**0.02**	22.2±15.0	14.7±11.2	0.19
Measures of Diastolic Function						
MV E/A	2.1±0.4	2.0±0.4	0.52	2.2±0.4	2.1±0.6	0.52
Lateral Mitral E/e′	6.0±1.5	7.0±1.7	0.14	6.2±1.0	6.5±1.8	0.6
Medial Mitral E/e′	8.1±1.6	9.6±2.5	0.1	8.4±1.8	9.2±1.9	0.33
TV E/A	1.7±0.3	1.6±0.4	0.85	1.8±0.3	1.7±0.5	0.42
Tricuspid Valve E/e′	4.6±1.4	5.0±1.8	0.55	5.0±1.4	4.8±2.1	0.86
Measures of Systolic Function						
LV SF (%)	38.1±4.2	39.4±6.5	0.56	36.6±2.9	37.3±9.5	0.81
LV EF (%)	59.9±4.5	60.6±5.0	0.72	58.8±4.6	57.4±5.1	0.49
Tei Index-Lateral Mitral	0.539±0.134	0.507±0.109	0.51	0.523±0.116	0.580±0.266	0.49
Tei Index-Medial Mitral	0.511±0.118	0.540±0.09	0.5	0.528±0.08	0.545±0.087	0.64
Tei Index-Tricuspid Valve	0.481±0.101	0.546±0.134	0.19	0.547±0.137	0.554±0.157	0.89
Hemodynamic Parameter						
HR(bpm)	76.0±9.4	82.7±7.0	0.06	67.3±8.4	73.4±7.2	0.07

Laboratory Value	Male Pre	Female Pre	P-Value	Male Post	Female Post	P-Value
SV(ml)	73.6±21.9	61.8±13.8	0.13	62.8±16.1	65.6±21.3	0.72
CI(L/min/m2)	3.3±0.6	3.3±0.9	0.92	2.5±0.6	3.1±0.9	**0.05**
MAP(mmHg)	79.3±6.5	80.1±7.1	0.78	81.8±9.6	81.5±5.8	0.93
TR Jet (m/s)	2.4±0.4	2.0±0.3	**0.01**	2.3±0.2	2.0±0.3	**0.002**
PVRI (mmHg/(L/min/m^2))	5.6±2.7	3.2±1.2	**0.02**	6.7±2.6	3.2±1.6	**0.0007**
SVRI (mmHg/(L/min/m^2)	24.7±4.7	25.5±7.9	0.77	33.9±7.6	28.0±7.6	0.07
O_2 Delivery (ml/L/min/m^2)	433±92	418±87	0.69	406±84	490±160	0.13
NIRS (%)	49.1±10.2	46.0±8.2	0.45	42.6±10.4	52.5±8.6	**0.04**

Data are expressed as mean ± one standard deviation. LDH = lactate dehydrogenase, hsCRP = high sensitivity C-reactive protein, LV EF = left ventricle ejection fraction, LV SF = left ventricle shortening fraction, TR jet = tricuspid regurgitation jet, SVRI = systemic vascular resistance index, PVRI = pulmonary vascular resistance index, NIRS = near infrared spectroscopy

Table 3

Laboratory, diastolic function, systolic function and hemodynamic changes with transfusion in male, female and pooled groups.

	Male	Female	Combined
Laboratory Value	**Pre to Post Change**	**Pre to Post Change**	**Pre to Post Change**
White Blood Cell Count (K/uL)	0.1 ±0.7	−1.6 ±0.9	−0.8 ±0.6
Hemoglobin (g/dL)	**2.3 ±0.2**	**2.2 ±0.3**	**2.3 ±0.2**
Hematocrit (%)	**6.3 ±0.7**	**5.3 ±1.0**	**5.8 ±0.6**
Platelet Count (K/uL)	−11.8 ±15.0	*−27.5 ±15.2*	*−20.0 ±10.6*
Hemoglobin S (%)	**−6 ±2.7**	**−4.8 ±1.1**	**−5.4 ±1.4**
Reticulocyte Count (%)	**−4.4 ±0.8**	**−3.8 ±1.2**	**−4.0 ±0.7**
LDH (U/L)	−68.3 ±62.9	−31.9 ±41.6	−49.3 ±36.4
hsCRP (mg/L)	*−4.4 ±2.1*	0.4 ±2.3	−1.9 ±1.6
Arginine:Ornithine	−0.1 ±0.1	0.2 ±0.2	0.0 ±0.1
Plasma Free Hemoglobin (mg/dL)	−4.2 ±5.8	1.8 ±5.8	−1.5 ±4.1
Measures of Diastolic Function			
Mitral Valve E/A	0.2 ±0.1	0.2 ±0.1	**0.2 ±0.1**
Lateral Mitral E/e′	0.2 ±0.5	−0.1 ±0.5	0.04 ±0.33
Medial Mitral E/e′	0.3 ±0.3	0.0 ±0.5	0.2 ±0.3
Tricuspid Valve E/A	0.2 ±0.1	0.0 ±0.1	0.1 ±0.1
Tricuspid Valve E/e′	0.3 ±0.4	−0.4 ±0.5	0.04 ±0.34
Measures of Systolic Function			
LV SF (%)	−1.6 ±1.2	−2.0 ±2.1	−1.8 ±1.2
LV EF (%)	−1.2 ±2.0	−3.1 ±1.6	−2.2 ±1.2
Lateral Mitral Tei Index	−0.016 ±0.052	0.079 ±0.064	0.033 ±0.042
Medial Mitral Tei Index	0.004 ±0.036	0.007 ±0.034	0.006 ±0.024
Tricuspid Valve Tei Index	0.066 ±0.057	0.028 ±0.049	*0.046 ±0.037*
Hemodynamics			
Heart Rate (bpm)	**−8.8 ±2.6**	**−8.6 ±1.3**	**−8.7 ±1.4**
Stroke Volume (ml)	**−10.8 ±4.9**	3.2 ±3.6**	−3.6 ±3.3
Cardiac Index(L/min/m^2)	**−0.8 ±0.3**	−0.2 ±0.2*	**−0.5 ±0.2**
Systolic Blood Pressure (mmHg)	−0.3 ±3.2	−2.8 ±3.3	−1.6 ±2.3
Diastolic Blood Pressure (mmHg)	3.8 ±3.4	3.2 ±2.6	*3.5 ±2.1*
Mean Arterial Pressure (mmHg)	2.5 ±2.9	1.6 ±2.4	2.0 ±1.8
TR Jet (cm/s)	−6.8 ±8.4	−3.0 ±6.3	−4.8 ±5.1
SVRI (mmHg/(L/min/m^2)	**9.2 ±2.5**	2.5 ±1.8**	**5.7 ±1.6**
PVRI (mmHg/(L/min/m^2))	**1.2 ±0.5**	0.2 ±0.4	*0.6 ±0.3*
Oxygen Delivery (ml/L/min/m^2)	−26.7 ±34.7	**70.8 ±30.6****	24.0 ±24.6
NIRS (%)	−5.4 ±4.2	4.1 ±1.8*	−0.6 ±2.5

Significant pre to post transfusion changes ($p < 0.05$) are indicated by bold type while trends ($0.05 < p < 0.10$) are italicized.

* indicates a trend difference between male and female patients ($0.05 < p < 0.10$),

** indicates a significant difference ($p < 0.05$).

LDH = lactate dehydrogenase, hsCRP = high sensitivity C-reactive protein, LV EF = left ventricle ejection fraction, LV SF = left ventricle shortening fraction, TR jet = tricuspid regurgitation jet, SVRI = systemic vascular resistance index, PVRI = pulmonary vascular resistance index, NIRS = near infrared spectroscopy