The Effect of Transfusion of Blood Products on Ventricular Assist Device Support Outcomes

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<u>Abstract</u>

Aims: Peri-operative blood transfusions are common among patients undergoing left ventricular assist device (LVAD) implantation. The association between blood product transfusion at the time of LVAD implantation and mortality has not been described.

Methods: This was a retrospective cohort study of all patients who underwent continuous flow LVAD implantation at a single, large, tertiary care, academic center, from 2008 to 2014. We assessed used of packed red blood cells (pRBC), platelets and fresh frozen plasma (FFP). Outcomes of interest included all-cause mortality and acute right ventricular (RV) failure. Standard regression techniques were used to examine the association between blood product exposure and outcomes of interest.

Results: A total of 170 patients were included in this study (mean age: 56.5 ± 15.5 years, 79.4% men). Over a median follow-up period of 11.2 months, for every unit of pRBC transfused, the hazard for mortality increased by 4% (HR 1.04; 95% CI 1.02 – 1.07) and odds for acute RV failure increased by 10% (OR 1.10; 95% CI 1.05 – 1.16). This association persisted for other blood products including platelets (HR for mortality per unit 1.20; 95% CI 1.08 – 1.32) and FFP (HR for mortality per unit 1.08; 95% CI 1.04 – 1.12). The most significant predictor of perioperative blood product exposure was a lower pre-implant hemoglobin.

Conclusions: Peri-operative blood transfusions among patients undergoing LVAD implantation were associated with a higher risk for all-cause mortality and acute RV failure. Of all blood products, FFP use was associated with worst outcomes. Future studies are needed to evaluate whether pre-implant interventions, such as intravenous iron supplementation, will improve the outcomes of LVAD candidates by decreasing need for transfusions.

Keywords: Left ventricular assist device, right ventricular failure, transfusions

Left ventricular assist devices (LVADs) have emerged as one of the main therapies for advanced heart failure, with more than 18,000 continuous flow devices implanted in the United States to date.(1) While these devices improve survival and quality of life in end-stage HF patients, the concomitant hemolysis, platelet dysfunction, von Willebrand factor degradation, need for anticoagulation and higher risk for bleeding predisposes these patients to anemia, bleeding and blood transfusions.(2-4) An increasing body of evidence now supports adverse events with blood transfusions among patients undergoing surgical coronary artery revascularization.(5, 6) Whether peri-operative blood transfusions lead to an elevated risk state in patients undergoing LVAD implantation remains poorly described with the contemporary generation of devices.

The decision to transfuse blood in the peri-operative period is somewhat subjective and varies between institutions and among clinicians.(7-9) In these patients, packed red blood cell transfusions have been associated with increased risk for infections, right ventricular failure, multi-organ dysfunction and increased risk for short term and long term mortality. This is possibly due to adverse events mediated by cytokine release and creation of a pro-inflammatory state.(6) These observations have led to adoption of more conservative peri-operative transfusion strategies in patients undergoing surgical coronary revascularization.(10) Ostensibly, similar risks related to blood transfusions may also hold true for patients undergoing LVAD implantation. Furthermore, blood transfusions lead to sensitization, influencing listing and outcomes related to cardiac transplantation in patients receiving LVADs as a bridge to transplant. Therefore, identifying patients at risk for peri-operative transfusions during LVAD implantation may help with targeted strategies to reduce risk and need for transfusions.

Accordingly, the objective of this study was to examine the association between blood transfusions at the time of LVAD implant with outcomes. More specifically, we examined the association between blood transfusions within 24 hours of LVAD implant and subsequent risk for mortality and acute RV failure. We also evaluated the effect of blood transfusions on change in panel of reactive antibody (PRA). Finally, we identified factors pre-implant that were associated with peri-operative blood product exposure.

Methods

Study Population and Data Collection

This is a retrospective cohort study involving a single, large, tertiary care academic center. We included all consecutive patients who underwent continuous flow LVAD implantation at the Hospital of the University of Pennsylvania between the years 2008 and 2014. All records for inpatient hospitalization and outpatient visits were reviewed in detail by trained abstractors. Demographic, clinical, laboratory, peri-procedural and imaging data were collected via intensive chart review. The Institutional Review Board of the University of Pennsylvania approved the study protocol.

During the study period all patients received Heartmate 2 or HeartWare LVADs. Standard institutional protocol regarding post-operative anticoagulation and antiplatelet therapies were identical for both the devices. Post-operatively, heparin drip was initiated within 24 hours as soon as post-operative bleeding was controlled. Antiplatelet therapy consisted of aspirin 325mg which was initiated once the platelet counts were over 100,000 cells/mm³.

Exposure variables

Data on transfusion of all blood products administered peri-operatively including packed red blood cells (pRBC), fresh frozen plasma (FFP) and platelets were collected. We divided patients into 2 groups based on median number of pRBCs transfused peri-operatively. Patients in the low transfusion group received pRBCs lesser than or equal to the median for the study population and patients in the high transfusion group received pRBC more than the median for the study population. **At our center, patients listed for transplant receive leucodepleted products. We also attempt to transfuse products from a single donor when feasible.**

Outcomes

Our primary outcome of interest was all-cause mortality over follow-up. Secondary outcomes included acute right heart failure after LVAD implantation during the index hospitalization, defined in accordance to previous studies as post-implantation use of inotropic therapy beyond 14 days or the need for Right Ventricular Assist Device (RVAD) implantation.(11)

We also assessed the association between blood transfusions and change in PRA in patients receiving LVAD as a bridge to transplant therapy. Change in PRA was defined as the either no change or increase in PRA at 6 months follow-up compared to pre-implant. PRA was analyzed at the core labs of the University of Pennsylvania using flow cytometry with bead targets.

Covariates

Potential confounders for the association between blood transfusion with all-cause mortality at follow-up were included based on clinical rationale and prior studies.(12) Demographic covariates included age, sex and race (Caucasian vs. other). Clinical covariates included preimplant body mass index, coronary artery disease, chronic lung disease, diabetes mellitus, history

of smoking, hypertension, dyslipidemia, atrial fibrillation, stroke, pulmonary hypertension, chronic renal disease, HF etiology (ischemic vs. non ischemic) and pre-implant INTERMACS score. Laboratory data included baseline hemoglobin, hemoglobin at 24 hours after implant and at discharge, pre-implant platelets, pre-implant MELD score and pre-implant creatinine. Implantation characteristics included indication for LVAD, prior cardiothoracic surgery, cardiopulmonary bypass time, other concomitant surgery performed and blood pressure and heart rate immediately prior to implant. Indication for LVAD was classified as bridge to transplant, destination therapy, bridge to recovery or bridge to decision. Echo characteristics prior to LVAD implant included left ventricular ejection fraction, right ventricular function, severity of tricuspid and mitral regurgitation. Left ventricular ejection fraction was treated as a continuous variable and the other echocardiographic variables were treated as ordinal variables (categorized as none/trivial, mild, moderate or severe).

Statistical analysis

Study cohort was divided into 2 groups based on the number of pRBCs transfused as defined above. Continuous variables were compared between groups using *t* test. Categorical variables were compared using the chi square test. All continuous variables are represented as mean \pm standard deviation unless otherwise indicated.

Association between transfusion and mortality: Kaplan Meier survival curves were generated for the study cohort by group based on the number of pRBCs transfused. The relationship between pRBC transfusion and all-cause mortality at follow-up was assessed using a Cox proportional hazards model adjusted for covariates listed above. For this analysis, number of pRBCs was entered into the model as a continuous variable. This model was also adjusted for

pre-implant hemoglobin. The proportional hazards assumption was evaluated and found to be met. In all analyses, patients were censored if they died, underwent a cardiac transplant, had a device explant due to myocardial recovery, were lost to follow-up or reached the end of the follow-up period (Dec 1, 2017). Since in clinical practice, patients listed for cardiac transplantation have a higher threshold for transfusion to prevent sensitization, we performed additional sensitivity analysis by excluding patients who underwent subsequent heart transplantation.

Association between transfusion and early RV failure: To examine the association between blood transfusion and early right ventricular failure, we fitted a logistic regression model with the number of pRBC transfused during index hospitalization as the independent variable adjusted for covariates described above.

Association between transfusion and PRA: We assessed the association between change in PRA and blood product transfusion using a logistic regression model. The change in PRA was modeled as a categorical variable.

Predictors of peri-implant blood product transfusion: Next, to assess predictors of blood product transfusion, each of the covariates were tested for their univariate association with blood product transfusion and were dropped from the initial model for a p>0.20. The remaining variables were entered into a linear regression model and eliminated for p>0.20. Age at implant, race and sex were forced into the model.

All analyses were performed using Stata software (version 11.0; StataCorp LP, College Station, TX). All analyses were two-sided and a p value less than 0.05 was considered significant.

Results

Study Population. A total of 170 patients were included in this study (mean age: 56.5 ± 15.5 years, 79.4% men). Five patients (2.9%) were lost to follow-up. The median follow-up duration for the entire cohort was 11.2 months (IQR 2.0 – 32.2). During the follow up period, 90 (52.9%) patients died, 49 (28.8%) patients underwent cardiac transplantation, 1 (0.6%) patient underwent an explant and 11 (6.5%) patients had a pump exchange.

The mean hemoglobin levels were 11.1 ± 1.9 g/dl at the time of LVAD implant and 11.3 ± 1.7 g/dl at 3 months. A total of 134 (78.8%) patients had pre-implant anemia according to the WHO definition (hemoglobin less than 12g/dL in females and less than 13g/dL in males): this included 80% females (n = 28) and 78.5% males (n=106).

Overall, 125 patients (73.5%) patients were transfused at least 1 unit of pRBC. Transfusion of both FFP and platelets was less common with 89 (52.3%) patients and 60 (35.3%) patients receiving them respectively. The median number of pRBCs transfused was 3 (IQR 0 - 10), median units of FFP transfused was 1 (IQR 0 - 4) and median number of platelets transfused was 0 (IQR 0 - 1).

Table 1 summarizes baseline characteristics of the study cohort stratified into low and high transfusion groups. Low transfusion group was defined as patients receiving lesser than or equal to the median number of pRBCs transfused for the entire cohort (3 units in our cohort) and high transfusion group comprised of patients transfused more than the median number of pRBCs transfused for the cohort. As compared to patients in the low transfusion group, patients in the high transfusion group were more likely to have a redo sternotomy, lower baseline hemoglobin, higher baseline creatinine and longer bypass time. Supplemental Table 1 summarizes baseline characteristics of patients stratified by number of pRBCs.

Peri-operative blood product transfusion and all-cause mortality

Figure 1 shows the Kaplan Meier curves for the study cohort stratified by low and high transfusion groups. Over a median follow-up duration of 11.2 months, patients in the high transfusion group had a lower survival as compared to patients in the low transfusion group (60% vs. 45.9%; unadjusted HR 1.71; 95% CI 1.12 – 2.62). This association persisted following multivariable adjustment with the hazard for mortality increasing by 4% for every unit of pRBC transfused (adjusted HR 1.04; 95% CI 1.02 – 1.07). Results of this multivariable adjusted Cox proportional hazards model are shown in Table 2.

Table 3 shows the unadjusted and adjusted association between transfusion of other blood products and all-cause mortality at follow-up.

In our sensitivity analyses, after excluding patients who underwent cardiac transplant, the association between mortality and blood product exposure peri-operatively remained statistically significant.

Peri-operative Blood Product Transfusions and Acute Right Ventricular Failure.

Over a median follow-up duration of 11.2 months, 32 patients (18.8%) had acute right ventricular failure. In our multivariable adjusted logistic regression model, peri-operative pRBC transfusion was associated with a higher odds of acute right ventricular failure (OR 1.10 per unit pRBC; 95% CI 1.05 – 1.16; Table 3). This association between acute right ventricular failure and blood product transfusion persisted for FFP (OR 1.09; 95% CI 1.01 – 1.18) and platelets (OR 1.67; 95% CI 1.23 – 2.27). Notably, 23 (71.9%) patients with RV failure also had acute renal injury, as defined by an increase in creatinine by >0.3mg/dL from pre-implant creatinine.

Blood Transfusions and PRA

In the 45 BTT patients, median pre-implant PRA was 0 (interquartile range 0 - 0%; mean \pm SD was 13.7 \pm 31.4%) and median post-implant PRA was 0 (Interquartile range 0-47%; mean \pm SD 26.7 \pm 37.9%). Overall, 27 patients (60%) had no change in their PRA and the remaining 18 patients (40%) had an increase in their PRA by 32.4 \pm 28.6%. There was no association between change in PRA and peri-operative exposure to blood products (OR 1.02; 95% CI 0.93 – 1.10) and this did not vary by gender (OR for PRA change in males compared to females 0.30; 95% CI 0.08 – 1.12). Figure 2 shows the change in PRA pre and post-implant and by gender.

Predictors of blood product exposure

Significant predictors of peri-operative blood product exposure in the univariate analyses included age, male sex, Caucasian race, atrial fibrillation, pre-implant hemoglobin, pre-implant IABP use, pre-implant RV dysfunction, pre-implant mitral regurgitation and intra-operative cardiopulmonary bypass time.

In the stepwise forward regression model, characteristics that remained predictive of perioperative blood product exposure were a lower pre-implant hemoglobin and male sex (model adjusted R² 0.11; p =0.0001; Table 4)

Discussion

In this large, single-center cohort study, we found that peri-operative blood product transfusions were associated with a higher subsequent risk for all-cause mortality and early RV

failure. Over a median follow-up duration of 11.2 months, for every unit of pRBC transfused perioperatively, the hazard for mortality increased by 4% and odds for acute RV failure increased by 10%. This association remained consistent for other type of blood products as well, with transfusion of platelets being associated with the highest risk for mortality and acute RV failure. Significant predictors of peri-operative blood product transfusions included lower pre-implant hemoglobin and male sex.

Peri-operative bleeding requiring blood transfusions are common during cardiac surgeries, especially with complex surgeries such as LVAD implantation.(2) Increasing evidence suggests that blood transfusions in cardiac surgical procedures are associated with worse outcomes and higher rates of complications with a detectable impact of as little as one or two units of pRBC increasing morbidity and mortality in patients undergoing coronary artery bypass graft (CABG).(13) However, the association between blood transfusion and adverse outcomes remains controversial with other studies showing that a restrictive transfusion strategy is not superior to liberal transfusion strategy. (14-16) In our study, the number of perioperative blood transfusions unfavorably correlated with long term survival and correlated with short term consequences such as acute RV failure as well. We also observed that a high proportion of patients had acute kidney injury associated with RV failure, likely secondary to cardiorenal syndrome with venous congestion reducing renal perfusion pressure. Our results are supported by Schaffer et al. who showed an absolute decrease in one year survival of 22% in patients receiving more than 5 pRBC compared with patients receiving \leq 5 units.(17) Similarly, in the study by Matthews et al, peri-operative transfusion was associated high mortality, RV failure and mortality in a cohort of patients predominantly undergoing implantation of HeartMate XVE.(12) Results of these studies and ours raise the question if a more complex pathophysiology beyond acute volume loading of

the RV, such as cytokine activation or impaired nitric oxide (NO) bioavailability, adversely affect right ventricular function.(18)

Our results also show a significant increase in the PRA following LVAD implantation. This is not unexpected considering the large number of blood products given to LVAD patients during the implantation. However, our data reveals no correlation between the number of transfusions and the change in PRA, likely due to lack of statistical power or due to uniform use of irradiated blood products at our center in this patient population.

In our study, the most significant predictor of peri-operative transfusion was low pre-implant hemoglobin despite inclusion of other clinically relevant variables such as the MELD score. This highlights the impact of pre-implant anemia as a risk factor for adverse events post-operatively after LVAD implantation. Accordingly, consistent with the recommendations provided by the Society of Thoracic Surgeons Workforce on blood conservation for patients undergoing cardiac procedures,(10) if feasible, pre-implant anemia should be corrected aggressively. Furthermore, transfusion according to a set hemoglobin level as the trigger for RBC transfusion is not supported by our study as adverse events correlated with transfusions despite adjusting for pre-implant hemoglobin. More restrictive blood transfusion strategies have been shown to be beneficial in critically ill, non-cardiac patients in randomized trial(19) and is potentially supported by our study in patients undergoing LVAD implantation as well.

Apart from pre-operative optimization of anemia, intra-operative strategies to minimize blood loss should also be considered. This includes paying meticulous attention to blood conserving and transfusion avoiding strategies such as avoidance of hemodilution by fluid infusion, use of closed extracorporeal circuit, autologous priming of the cardiopulmonary circuit and maintenance of normothermia during cardiopulmonary bypass to reduce postop bleeding.(20) Choice of cardiopulmonary bypass circuits in patients needing a redo sternotomy for LVAD implantation should also be carefully considered to minimize intraoperative time. These strategies are currently endorsed by the European Association of Cardiothoracic surgery. Findings from our study also helps highlights high-risk factors for transfusion, such as older age facilitating more targeted use of such strategies.

Limitations

The findings of our study should be interpreted in the light of several considerations. First, our study is a retrospective observational study **and hence we cannot imply causality**. Although we adjusted for a variety of clinically significant variables in our statistical models, residual confounding cannot be eliminated. Our dataset did not capture variables such as use of aspirin, temporary mechanical circulatory support use, need for surgical revision for bleeding, **hemodynamic parameters and echo parameters such as tricuspid regurgitation, length of time blood products were stored for** etc. Nonetheless, the results of our study reflect "real-world practice". Second, our cohort comprised of patients at a single center thus limiting generalizability and reflecting practice at a single center. However, we collected detailed pre and post-implant data that is typically not available in administrative datasets. Finally, for our sensitivity analysis looking at the association between blood product transfusion and change in PRA, we did not have data on all patients considered to be transplantable but only on patients who underwent a complete transplant evaluation. Accordingly, the number of patients included in this analysis was small limiting its power.

In conclusion, peri-operative blood product transfusions were highly prevalent in this study of patients with advanced heart failure receiving continuous flow LVAD therapy and correlated with long-term mortality as well as acute RV failure. The strongest predictor of peri-operative transfusion was low pre-implant hemoglobin, suggesting that transfusion strategies are still set to a particular hemoglobin level and potentially correcting pre-implant anemia aggressively, if feasible, may lead to improved outcomes. Future studies are needed to evaluate strategies that target focus at decreasing the number of blood transfusions in patients undergoing LVAD implantation.

<u>References</u>:

1. Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Myers SL, Miller MA, Baldwin JT, Young JB. Seventh INTERMACS annual report: 15,000 patients and counting. *J Heart Lung Transplant*. 2015 Dec;**34**(12):1495-1504.

2. Genovese EA, Dew MA, Teuteberg JJ, Simon MA, Kay J, Siegenthaler MP, Bhama JK, Bermudez CA, Lockard KL, Winowich S, Kormos RL. Incidence and patterns of adverse event onset during the first 60 days after ventricular assist device implantation. *Ann Thorac Surg.* 2009 Oct;**88**(4):1162-1170.

3. Miller LW, Pagani FD, Russell SD, John R, Boyle AJ, Aaronson KD, Conte JV, Naka Y, Mancini D, Delgado RM, MacGillivray TE, Farrar DJ, Frazier OH, HeartMate IICI. Use of a

continuous-flow device in patients awaiting heart transplantation. *N Engl J Med.* 2007 Aug 30;**357**(9):885-896.

4. Aaronson KD, Slaughter MS, Miller LW, McGee EC, Cotts WG, Acker MA, Jessup ML, Gregoric ID, Loyalka P, Frazier OH, Jeevanandam V, Anderson AS, Kormos RL, Teuteberg JJ, Levy WC, Naftel DC, Bittman RM, Pagani FD, Hathaway DR, Boyce SW, HeartWare Ventricular Assist Device Bridge to Transplant ATI. Use of an intrapericardial, continuous-flow, centrifugal pump in patients awaiting heart transplantation. *Circulation*. 2012 Jun 26;**125**(25):3191-3200.

 Engoren MC, Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ. Effect of blood transfusion on long-term survival after cardiac operation. *Ann Thorac Surg.* 2002 Oct;**74**(4):1180-1186.

6. Murphy GJ, Reeves BC, Rogers CA, Rizvi SI, Culliford L, Angelini GD. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. *Circulation*. 2007 Nov 27;**116**(22):2544-2552.

7. Bracey AW, Radovancevic R, Riggs SA, Houston S, Cozart H, Vaughn WK, Radovancevic B, McAllister HA, Jr., Cooley DA. Lowering the hemoglobin threshold for transfusion in coronary artery bypass procedures: effect on patient outcome. *Transfusion*. 1999 Oct;**39**(10):1070-1077.

8. Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Abraham E, MacIntyre NR, Shabot MM, Duh MS, Shapiro MJ. The CRIT Study: Anemia and blood transfusion in the critically ill--current clinical practice in the United States. *Crit Care Med.* 2004 Jan;**32**(1):39-52.

9. Vincent JL, Baron JF, Reinhart K, Gattinoni L, Thijs L, Webb A, Meier-Hellmann A, Nollet G, Peres-Bota D, Investigators ABC. Anemia and blood transfusion in critically ill patients. *JAMA*. 2002 Sep 25;**288**(12):1499-1507.

Society of Thoracic Surgeons Blood Conservation Guideline Task F, Ferraris VA, Brown JR, Despotis GJ, Hammon JW, Reece TB, Saha SP, Song HK, Clough ER, Society of Cardiovascular Anesthesiologists Special Task Force on Blood T, Shore-Lesserson LJ, Goodnough LT, Mazer CD, Shander A, Stafford-Smith M, Waters J, International Consortium for Evidence Based P, Baker RA, Dickinson TA, FitzGerald DJ, Likosky DS, Shann KG. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. *Ann Thorac Surg*. 2011 Mar;**91**(3):944-982.

11. Raina A, Seetha Rammohan HR, Gertz ZM, Rame JE, Woo YJ, Kirkpatrick JN.
Postoperative right ventricular failure after left ventricular assist device placement is predicted
by preoperative echocardiographic structural, hemodynamic, and functional parameters. *J Card Fail.* 2013 Jan;**19**(1):16-24.

12. Matthews JC, Pagani FD, Haft JW, Koelling TM, Naftel DC, Aaronson KD. Model for end-stage liver disease score predicts left ventricular assist device operative transfusion requirements, morbidity, and mortality. *Circulation*. 2010 Jan 19;**121**(2):214-220.

Paone G, Likosky DS, Brewer R, Theurer PF, Bell GF, Cogan CM, Prager RL,
 Membership of the Michigan Society of T, Cardiovascular S. Transfusion of 1 and 2 units of red
 blood cells is associated with increased morbidity and mortality. *Ann Thorac Surg.* 2014
 Jan;97(1):87-93; discussion 93-84.

Murphy GJ, Pike K, Rogers CA, Wordsworth S, Stokes EA, Angelini GD, Reeves BC,
 Investigators TI. Liberal or restrictive transfusion after cardiac surgery. *N Engl J Med*. 2015 Mar 12;372(11):997-1008.

15. Shehata N, Mistry N, da Costa BR, Pereira TV, Whitlock R, Curley GF, Scott DA, Hare GMT, Juni P, Mazer CD. Restrictive compared with liberal red cell transfusion strategies in cardiac surgery: a meta-analysis. *Eur Heart J*. 2019 Apr 1;**40**(13):1081-1088.

16. Mazer CD, Whitlock RP, Fergusson DA, Hall J, Belley-Cote E, Connolly K, Khanykin B, Gregory AJ, de Medicis E, McGuinness S, Royse A, Carrier FM, Young PJ, Villar JC, Grocott HP, Seeberger MD, Fremes S, Lellouche F, Syed S, Byrne K, Bagshaw SM, Hwang NC, Mehta C, Painter TW, Royse C, Verma S, Hare GMT, Cohen A, Thorpe KE, Juni P, Shehata N, Investigators T, Perioperative Anesthesia Clinical Trials G. Restrictive or Liberal Red-Cell Transfusion for Cardiac Surgery. *N Engl J Med.* 2017 Nov 30;**377**(22):2133-2144.

17. Schaffer JM, Arnaoutakis GJ, Allen JG, Weiss ES, Patel ND, Russell SD, Shah AS, Conte JV. Bleeding complications and blood product utilization with left ventricular assist device implantation. *Ann Thorac Surg.* 2011 Mar;**91**(3):740-747; discussion 747-749.

18. Donadee C, Raat NJ, Kanias T, Tejero J, Lee JS, Kelley EE, Zhao X, Liu C, Reynolds H, Azarov I, Frizzell S, Meyer EM, Donnenberg AD, Qu L, Triulzi D, Kim-Shapiro DB, Gladwin MT. Nitric oxide scavenging by red blood cell microparticles and cell-free hemoglobin as a mechanism for the red cell storage lesion. *Circulation*. 2011 Jul 26;**124**(4):465-476.

19. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E. A multicenter, randomized, controlled clinical trial of transfusion

requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med.* 1999 Feb 11;**340**(6):409-417.

Pagano D, Milojevic M, Meesters MI, Benedetto U, Bolliger D, von Heymann C,
 Jeppsson A, Koster A, Osnabrugge RL, Ranucci M, Ravn HB, Vonk ABA, Wahba A, Boer C.
 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. *Eur J Cardiothorac Surg.* 2018 Jan 1;53(1):79-111.

Table 1: Baseline characteristics of the study table stratified by number of packed red blood cells transfused (pRBC)

Baseline characteristics	Low transfusion group	High transfusion group	P value
	(0-3 U of pRBC	(more than 3 units of	
	transfused, n=85)	pRBCs transfused, n=85)	
Age, years	54.6 + 15.4	58.3 <u>+</u> 15.4	0.11
Male	67 (78.8%)	68 (80.0%)	0.85
Race			0.50
Caucasian	36 (42.4%)	42 (49.4%)	
African-american	16 (18.8%)	16 (18.8%)	
Unknown	31 (36.5%)	24 (28.2%)	
Other	2 (2.3%)	3 (3.5%)	
Diabetes	38 (44.7%)	40 (47.1%)	0.76
Hypertension	47 (55.3%)	54 (63.5%)	0.27
Dyslipidemia	53 (62.3%)	56 (65.9%)	0.63
Chronic renal insufficiency	30 (35.3%)	31 (36.5%)	0.74
Ischemic cardiomyopathy	36 (42.3%)	44 (51.8%)	0.14
BMI	29.8 <u>+</u> 6.8	29.3 <u>+</u> 7.2	0.76
Pulmonary hypertension	31 (36.5%)	27 (31.8%)	0.55
COPD	15 (17.6%)	14 (16.5%)	0.81
Smoking	32 (37.6%)	36 (42.3%)	0.53
Atrial fibrillation	31 (36.5%)	40 (47.1%)	0.16
Stroke	12 (14.1%)	11 (12.9%)	0.38
Prior CT surgery	21 (24.7%)	36 (42.3%)	0.01
LVAD type			0.39
HM2	70 (82.3%)	74 (87.1%)	
HVAD	15 (17.7%)	11 (12.9%)	
Indication for LVAD			0.30
Bridge to transplant	35 (41.1%)	30 (35.3%)	
Bridge to decision	9 (10.6%)	7 (8.2%)	
Destination therapy	37 (43.5%)	47 (55.3%)	
Bridge to recovery	4 (4.7%)	1 (1.2%)	
INTERMACS score			0.14
1	12 (14.1%)	23 (27.1%)	
2 3	21 (24.7%)	20 (23.5%)	
	26 (30.6%)	16 (18.8%)	
4	11 (12.9%)	13 (15.3%)	
5	0 (0)	1 (1.2%)	
Pre-implant heart rate, bpm	85 <u>+</u> 16	83 <u>+</u> 17	0.05
Pre-implant systolic blood	99 <u>+</u> 16	100 <u>+</u> 15	0.83
pressure, mmHg			

Pre-implant diastolic blood	63 <u>+</u> 11	60 <u>+</u> 10	0.06
pressure			
Baseline hemoglobin (g/dL)	11.6 <u>+</u> 1.9	10.7 <u>+</u> 1.8	< 0.01
Baseline Platelets,	182.2 <u>+</u> 63.9	193.9 <u>+</u> 74.3	0.27
cells/microliter			
Baseline creatinine, mg/dL	1.3 <u>+</u> 0.5	1.6 <u>+</u> 0.9	0.02
Baseline total bilirubin, mg/dL	1.3 <u>+</u> 0.66	1.3 <u>+</u> 0.96	0.74
Pre-op MELD score, median	12.6 (9.5 – 17.0)	13.7 (11.3 – 18.6)	0.13
(IQR)			
Baseline LV ejection fraction	15.9 <u>+</u> 7.8	16.0 <u>+</u> 6.7	0.93
Pre-implant tricuspid			0.11
regurgitation			
None/Trace	17 (20.0%)	11 (12.9%)	
Mild	27 (31.8%)	26 (30.6%)	
Moderate	33 (38.8%)	27 (31.8%)	
Severe	8 (9.4%)	10 (11.8%)	
Pre-implant mitral		, , , , , , , , , , , , , , , , ,	0.06
regurgitation			
None/trace	4 (4.7%)	12 (14.1%)	
Mild	18 (21.2%)	22 (25.9%)	
Moderate	38 (44.7%)	32 (37.6%)	
Severe	25 (29.4%)	14 (16.5%)	
Pre-implant right ventricular		, , , , , , , , , , , , , , , , ,	0.25
dysfunction			
None/trace	11 (12.9%)	7 (8.2%)	
Mild dysfunction	26 (30.6%)	21 (24.7%)	
Moderate dysfunction	38 (44.7%)	38 (44.7%)	
Severe dysfunction	9 (10.6%)	13 (15.3%)	
5			
Surgical cardiopulmonary	79 (66 – 95)	90 (71 – 125)	0.03
bypass time (minutes; median			
(IQR)			
Concomitant surgery	11 (12.9%)	12 (14.1%)	0.82
Abbreviations: BMI - body m	ass index, COPD - chi	ronic obstructive pulmonary	disease, CT
cardiothoracic surgery, HM2 -	Heart Mate 2, HVAD –	HeartWare, IQR - interquarti	le range, LV
left ventricle, LVAD - left vent	ricular assist device, ME	LD – model for end stage live	er disease
Note: All continuous variables a	re expressed at mean \pm s	tandard deviation unless speci	fied otherwis
All categorical variables are exp	-		

Table 2: Results of multivariable adjusted Cox proportional hazards model examining association between transfusion of packed red blood cells (pRBC) and all-cause mortality at follow-up

Variable	Adjusted hazard ratio (95%	P value
	Confidence interval)	
pRBC transfusion (per unit increase)	1.04 (1.02 – 1.07)	0.001
Baseline hemoglobin, g/dL (per unit increase)	1.04 (0.88 – 1.24)	0.62
Age, in years (per unit increase)	1.05 (1.02 – 1.07)	<0.001
Male sex	2.23 (0.91 – 5.46)	0.08
Pre-implant body mass index, kg/m ² (per unit	1.06 (1.01 – 1.12)	0.04
increase)		
Diabetes Mellitus	0.59 (0.32 – 1.07)	0.08
Chronic lung disease	0.47 (0.21 – 1.04)	0.06
Pulmonary hypertension	1.74 (0.94 – 3.25)	0.08
History of smoking	1.05 (0.61 – 1.81)	0.86
Atrial fibrillation	0.69 (0.39 – 1.23)	0.21
Intra-operative cardiopulmonary bypass time,	1.00 (0.99 – 1.01)	0.15
minutes (per unit increase)		
MELD score (per unit increase)	0.98 (0.93 – 1.03)	0.38

Pre-implant right ventricular dysfunction				
None	1.0 (Reference group)			
Mild	0.70 (0.26 - 1.94)	0.50		
Moderate	1.58 (0.62 - 4.04)	0.34		
Severe	2.44 (0.76 - 7.8-)	0.13		
INTERMACS score	0.96 (0.75 – 1.23)	0.76		
Other concomitant surgery	0.80 (0.32 - 1.98)	0.63		
Abbreviations: INTERMACS – Interagency Registry for Mechanically Assisted Circulatory				
Support; MELD – model for end stage liver disease; pRBC – packed red blood cell				

Product type	Transfusion units		Adjusted HR for mortality	Adjusted OR for acute right	
	Median (IQR)		per unit product	ventricular failure per unit product	
			transfused (95% CI)	transfused(95% CI)	
	Alive	Dead			
	(n = 80)	(n = 90)			
PRBC	2.5 (0 - 7)	5 (0 - 14)	1.04 (1.02 – 1.07)	1.10 (1.05 – 1.16)	
FFP	0 (0 – 2)	2 (0 – 5)	1.08 (1.04 – 1.12)	1.09 (1.01 – 1.18)	
Platelets	0 (0 – 1)	0 (0 – 1)	1.20 (1.08 – 1.32)	1.67 (1.23 – 2.27)	
Total blood	4 (1 – 9.5)	7 (2 – 18)	1.03 (1.01 – 1.04)	1.06 (1.03 – 1.09)	
product exposure					

Table 3: Association between peri-operative blood product exposure and outcomes

Variable	Unadjusted TBPE	P value	Adjusted TBPE <u>+</u>	P value
	\pm standard error		standard error	
Age, years	0.19 <u>+</u> 0.08	0.014	-	-
Caucasian Race	5.19 <u>+</u> 2.45	0.035	-	-
Male sex	5.58 <u>+</u> 3.04	0.07	9.611	0.002
Atrial fibrillation	4.51 <u>+</u> 2.49	0.072	-	-
Pre-op IABP	8.39 <u>+</u> 3.47	0.017	-	-
Pre-op RV	34.72 <u>+</u> 6.09	<0.0001	-	-
dysfunction				
Pre-op inotrope	1.65 <u>+</u> 2.51	0.51	-	-
Pre-implant	-2.03 <u>+</u> 0.62	0.001	-2.51	< 0.0001
hemoglobin				
Intra-operative	0.037 <u>+</u> 0.028	0.196	-	-
cardiopulmonary				
bypass time				

Table 4: Predictors of peri-operative blood product transfusion

<u>Figure 1 – Association between survival and peri-operative pRBC transfusion</u> Kaplan Meier curves showing survival of the study cohort stratified into 2 groups based on number of peri-operative packed red blood cell units transfused

Figure 2 – Change in panel reactive antibodies before and 3 months after LVAD implant: (a) For the entire cohort (b) Stratified by gender