

**TARGETED BLEEDING MANAGEMENT REDUCES THE
REQUIREMENT FOR BLOOD COMPONENT THERAPY IN LUNG
TRANSPLANT RECIPIENTS**

**Smith I¹, Pearse B^{1,2,3,4}, Faulke D¹, Naidoo R⁴, Nicotra L³, Hopkins P⁵,
Ryan E⁶**

Department of Anaesthesia, The Prince Charles Hospital, Brisbane, Queensland,
Australia 1

Centre of Health Practice Innovation, Griffith University, Brisbane, Queensland,
Australia 2

Adult Critical Care Services, The Prince Charles Hospital, Brisbane, Queensland,
Australia 3

Department of Cardiothoracic Surgery, The Prince Charles Hospital, Brisbane,
Queensland, Australia 4

Queensland Lung Transplant Service, The Prince Charles Hospital, Brisbane,
Queensland, Australia 5

Biostatistics Department, Institute of Psychiatry, Psychology & Neuroscience,
King's College London, UK 6

Study site: The Prince Charles Hospital, Brisbane, Queensland, Australia.

Corresponding author Dr Ian Smith, The Prince Charles Hospital, Rode Rd,
Chermside, Brisbane, QLD 4032, Australia; +61731394000;

ismith007@internode.on.net

TARGETED BLEEDING MANAGEMENT REDUCES THE REQUIREMENT FOR BLOOD COMPONENT THERAPY IN LUNG TRANSPLANT RECIPIENTS

ABSTRACT

Objective

Lung transplantation is associated with high rates of bleeding and frequent blood transfusion. We aimed to determine if point of care coagulation testing reduced transfusion requirements.

Design, Settings and Participants

A before-and-after cohort analysis conducted at a single tertiary referral centre. Ninety-three sequential adult patients between January 2010 and January 2014 undergoing isolated lung transplant without preoperative extracorporeal support were analysed.

Intervention

ROTEM and Multiplate point of care coagulation testing was introduced on July 1st 2012 with an associated algorithm based on the results.

Measurements and main results

Statistically significant decreases in the proportion of patients receiving PRBCs (87% vs. 65%; $p=0.015$), FFP (72% vs. 30%; $p<0.0001$) and platelets (70% vs. 37%; $p=0.002$) were found after the intervention. There were small decreases in median chest tube blood loss at two hours (300mls vs. 215mls; $p=0.03$) and four hours (440mls vs. 350mls; $p=0.050$) but not at twelve hours postoperatively. There were no changes in re-operation for bleeding (9% vs. 4%; $p=0.158$) or in-

hospital mortality (6% vs. 2%; $p=0.617$). The cost of blood products administered decreased from a median of \$3935 to \$991 ($p<0.001$).

Conclusion

Use of point-of-care coagulation testing in lung transplant surgery is associated with a significant reduction in blood product use and cost. There were no detectable changes in outcome besides from a small decrease in early postoperative bleeding.

Key words

Point of care coagulation testing, Blood transfusion, Lung transplantation

Introduction

The rate of allogeneic blood transfusion to treat bleeding complications in the bilateral sequential lung transplant (BSLT) population is poorly reported [1-3]. Managing bleeding with a liberal transfusion approach, particularly in this patient group, may negatively impact outcome. Cohort studies have demonstrated a dose dependent association of worse outcomes including transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO) and transfusion related immunomodulation (TRIM) [4-8] related to blood component therapy. TRIM increases the frequency and severity of viral and bacterial sepsis in an already immunosuppressed population with sepsis being a direct cause of acute lung injury [6]. Primary graft dysfunction (PGD) is a significant manifestation of acute lung injury, and is the greatest risk factor for death during the first year post-transplantation [9]. Large volume blood product use is associated with both an increased rate and severity of PGD, and is therefore an important modifiable risk factor [10]. Furthermore, blood transfusion may lead to the generation of anti-human lymphocyte antibodies, which may impact acute and chronic graft rejection, prospects for future re-transplantation and survival [3].

The benefits of transfusion are not well quantified. The ability of transfused packed red blood cells (PRBCs) to carry and deliver oxygen to tissues is impaired due to acquired structural and functional changes developing during storage [11]. Transfused platelets do not function normally, contributing less to hemostasis than anticipated [12]. The use of other pro-hemostatic agents including recombinant activated factor VII (rVIIa), prothrombin complex concentrates and tranexamic acid may increase the risk of thromboembolic events [13, 14].

We aimed to minimise unnecessary transfusion by implementing evidence based hemostasis management supported by point of care coagulation testing (POCCT). This study compares blood product use, patient outcomes and cost before and after implementation of this change in practice in lung transplant patients.

Methods

A retrospective before-and-after cohort analysis was performed on 93 patients over the age of 15 who underwent primary BSLT between January 2010 and January 2014 at a single centre tertiary referral hospital, The Prince Charles Hospital, in Brisbane, Australia. This study was approved by the institutional ethics committee (HREC/13/QPCH/310). The change in blood management practice commenced on July 1st 2012, with 47 patients receiving a lung transplant before the change and 46 after. A power analysis revealed that a baseline 80% rate of transfusion reducing to 50% transfusion would need a sample size of 39 in each arm to achieve a power of 80% at a significance level of 0.05. Exclusion criteria were limited to patients having concurrent procedures (e.g. valve or coronary surgery), multi-organ transplant, re-transplantation, or pre-transplant extracorporeal support. No single lung transplants were performed in the study period, and all transplants were conducted on cardiopulmonary bypass.

The primary end point of the study was the incidence of transfusion of autologous blood products. Secondary end points included the number of units of each blood product type, acquisition cost of blood products, unplanned re-exploration for bleeding, chest tube output and primary graft dysfunction. Data for mortality, ventilation time, and length of intensive care were also recorded along with the frequency of other haemostatic therapies including prothrombin complex concentrate (Prothrombinex VF, CSL Behring, Melbourne, Victoria Australia), recombinant factor VIIa use (rFVIIa; NovoSeven: Novo Nordisk, Bagsvaerd, Glaxo Denmark), and tranexamic acid (Cyklokapron, Pfizer, Pty Ltd, Perth, Australia).

Data were collected prospectively within the routine audit of the centre, with a dedicated audit team which did not include any clinicians or any of the authors, and were not associated with the point of care testing program. Pre- and intra-operative use of anticoagulants and pro-hemostatic agents were searched for within medication charts, anaesthetic charts and admission clerking documentation as relevant. Blood product information and laboratory values were sourced from the electronic blood banking/laboratory software, and cross-checked against anaesthetic or intensive care charts. Chest tube drainage were sourced from the intensive care computerised information system recorded contemporaneously by ICU nursing staff. Return to theatre events were sourced from the notes and cross-checked against computerised theatre records for each patient. In hospital mortality was sourced from the notes and the associated discharge summary for each patient. Where necessary, additional or missing information was checked by study authors by individual chart review.

Clinical management

During the two comparison periods the lung transplant program was supported unchanged by 3 surgeons and 10 anesthesiologists. All BSLTs at our institution are performed on cardiopulmonary bypass with a beating heart. The technique is standardised across all patients. Donor selection complies with international practice.

The surgical technique includes a midline sternotomy with central cannulation, cooling to 34 degrees and a pulmonary arterial vent. Weaning from bypass was achieved with a low inspired oxygen concentration (~30%) after lung recruitment with a protective ventilation strategy.

Point of Care Coagulation Testing

Whole blood coagulation assays Rotational Thromboelastometry (ROTEM®; Tem International GmbH, Munich, Germany) and impedance platelet aggregometry (Multiplate®; Verum Diagnostica GmbH, Munich, Germany), in conjunction with treatment algorithms are increasingly being used to guide bleeding management decisions in the surgical setting. Neither test utilises serum avoiding delays for blood centrifugation. ROTEM is a viscoelastic citrated whole blood coagulation assessment using a stationary cup and a moving pin. Changes in rotational forces between the pin and cup occur with coagulation. Time to initiation of coagulation, acceleration of coagulation, maximum clot strength and presence of fibrinolysis can all be detected within minutes in the presence of different activators. The Multiplate uses thrombin inhibited whole blood in an impedance aggregometry test. An electrical current is passed between two pairs of electrodes and as platelets adhere resistance rises. Both these tests provide clinicians with rapid and comprehensive information for diagnosing and targeting specific hemostatic defects and can be performed in the operating theatre [15, 16].

Hemostatic Management

ROTEM assays were performed at various time points. In the event of continued bleeding after protamine administration, a ROTEM was standard of care. Multiplate and ROTEM were also conducted at the discretion of the anesthesiologist after induction of anaesthesia and on rewarming in high risk patients. Tests were repeated after administration of products if bleeding continued.

The heparin was reversed with protamine with an initial dose of approximately 0.8mg per 100 units of total heparin administered, with further doses of approximately 0.2mg per 100 units of total heparin during administration of residual circuit blood. If bleeding continued after protamine administration, a treatment plan, following our previously described bleeding management treatment algorithm was followed (Figure 1) [15]. An abnormal ROTEM was not treated unless there was active bleeding. Prothrombinex complex concentrate was utilised to correct bleeding diathesis due to warfarin after rewarming. Dosing remained at the discretion of the anaesthetist but was guided by EXTEM results in the second cohort.

Cost analysis

The costs of blood products were calculated from the National Blood Authority of Australia website (all prices in Australian dollars) current from 1 July 2015 [17]. The current costs are \$374, \$304, \$387, and \$177 for packed red blood cells, fresh frozen plasma, platelet concentrate, cryoprecipitate per unit respectively. Factor concentrates costs included Prothrombinex complex concentrate at \$274 per 500IU, and recombinant factor VIIa at \$1283 per mg. All costs were considered as acquisition only, and do not include any costs of storage, cross-matching, thawing, administration or complications. Other costs included ROTEM and Multiplate testing at \$15.16 and \$11.23 per batch of testing. The cost of tranexamic acid is \$5.81 per 1gram ampoule at our hospital.

Statistical Analysis

Data are presented as means (\pm standard deviation (SD)), medians (with interquartile ranges (IQR)) and percentages as appropriate. Statistical calculations were performed in R version 2.15.2 for Windows (R Development Core Team, 2008, Vienna, Austria). The Wilcoxon signed-rank test was used to test for differences (before perioperative bleeding management compared to after perioperative bleeding management) for continuous non

parametric variables. Fisher's exact test was used to perform analysis of frequencies, and the binomial test was used to determine differences in proportions before perioperative bleeding management compared to after perioperative bleeding management. In all of the tests performed, a significance level of $\alpha = 0.05$ was used.

Results

A total of 100 patients underwent lung transplantation from January 2010 until January 2014. Seven patients were excluded; two due to preoperative ECMO, two due to combined heart-lung transplantation, and three due to concomitant valve or coronary surgery. Point of care coagulation testing was introduced in July 2012 and 47 patients before and 46 patients after this change in bleeding management practice were analysed and compared. The post POCCT cohort had a slightly lower INR at baseline (1.14 vs 1.08, $p=0.019$), but there were no other differences (Table 1). Preoperative and admission-to-ICU haemoglobins were similar with identical medians at 137 and 93g/L respectively with minor differences in quartiles ($p=0.58$ and 0.85). Similarly, postoperative ionised calcium levels were also not different with a median of 1.1mmol/L (IQR 1.00-1.15) vs 1.1mmol/L (1.00-1.20) ($p=0.056$).

Percentage Patients Receiving Allogeneic Blood Transfusion

The change in bleeding management practice resulted in statistically significant decreases in the proportion of patients receiving PRBCs (87% vs. 65%; $p=0.015$), FFP (72% vs. 30%; $p<0.0001$) and platelets (70% vs. 37%; $p=0.002$). A greater number of patients received cryoprecipitate but this did not reach statistical significance (21% vs. 37%; $p=0.114$).

Breakdown of Intra-Operative and Post-Operative Transfusion

Analysis of the intra-operative and post-operative time periods demonstrated reductions in the percentage of patients receiving intra-operative transfusions of PRBCs (77% vs. 52%; $p=0.018$), FFP (62% vs. 4.3%; $p<0.0001$) and platelets, (57% vs. 11%; $p<0.0001$); as well as the total number of units transfused of PRBCs (205 vs. 74; $p=0.0003$), FFP (167 vs. 5; $p=0.0001$) and platelets (65 vs. 8; $p=0.0001$) (Figure. 2). Cryoprecipitate transfusion had no significant changes in proportion (6% vs. 13%; $p=0.316$) or number of units (39 vs. 54; $p=0.294$).

Post-operatively we observed fewer significant changes in the percentage of patients receiving blood products. Transfusion of PRBCs (55% vs 35%; $p=0.061$), platelets (36% vs. 20%, $p=0.106$) and cryo (19% vs. 17%; $p=1.000$) were unchanged. Fresh frozen plasma transfusion decreased in terms of proportion (49% vs. 13%; $p<0.0001$) and number of units (107 vs. 19; $p=0.0001$). The number of PRBCs units transfused postoperatively was significantly reduced (179 vs.49; $p=0.0087$). Platelet and cryoprecipitate units transfused were unchanged (platelets 61 vs. 30; $p=0.0543$, cryo 65 vs. 94; $p=0.9047$).

Chest tube blood loss

There were statistically significant drops in median chest tube blood loss at both 2 hrs (300mls vs. 215mls; $p=0.03$) and 4 hours (440mls vs. 350mls; $p=0.050$). The median blood loss at 12 hours was not statistically significant (820ml vs. 765ml; $p=0.10$). One patient died after 2 hours in ICU from uncontrolled bleeding, in the group before the change in practice, therefore no blood loss was recorded in the measurement of subsequent time points. Six patients (4 pre change in practice and 2 post change in practice) returned to theatre due to bleeding, and blood loss time points after this were treated as missing observations.

Patient Outcomes

Despite reductions in transfusion, we could not detect any change in adverse outcomes noting the small numbers in each cohort. There were no changes to re-exploration for bleeding (four patients before vs two patients after, $p=0.158$) or in-hospital mortality (three vs one, $p=0.617$). There was no significant decrease in ICU length of stay (166 vs 116 hours, $p=0.698$) or initial median ventilation hours before, 19 hours (IQR 3–109) vs. after, 18.5 hours; (IQR 7–647); $p=0.857$).

Primary Graft Dysfunction

PGD grades 1 to 3 were examined at 24 hours, with PGD grades 1-2 grouped together as they required similar supportive therapies. Although fewer patients developed PGD grade 3 (six vs three) and more patients had no PGD (16 vs 19) after the change in bleeding management, none of these changes were significant ($p=0.684$).

Pro-hemostatic Interventions

There was a significant increase in the incidence of patients receiving tranexamic acid in the second time period (34% vs. 85%; $p < 0.0001$). We were unable to detect any differences between proportion of patients receiving prothrombin complex concentrates (13% vs 11%; $p=1.000$) and rFVIIa (4.3% vs 0%; $p=0.5$) before and after the change in practice, noting the low rate of use in each group.

Cost

Acquisition costs of blood products were significantly different between the two cohorts. The median (IQR) reduced from \$3935 (\$1803 to \$8928) to \$991 (\$374 to \$2513) (Figure 3). This result was statistically significant with a p-value of <0.001 . ROTEM tests were used a total of 235 times across the cohort for a cost of \$11900. Multiplate tests were used 78 times across the cohort for a cost of \$4000. Total tranexamic dose was not collected but the usual dose approximated 3g per patient. This drug costs our institution \$5.81/g, totalling \$278 and \$680 for each cohort respectively. The total spend

on each cohort considering blood product acquisition, point of care testing, and tranexamic acid use decreased from \$6640/patient before to \$2550/patient after the introduction of point of care testing.

Discussion

There is little recent data on the incidence of blood transfusion in lung transplantation surgery in the literature. A recent 10-year British case series using cardiopulmonary bypass found median transfusions of 3 units PRBCs, 2 units of FFP and 1 unit of platelets[18]. Other data is much older, with a 2006 study quoting means of 8 units PRBCs, 10 units FFP and 2 units of platelets for lung transplantation on cardiopulmonary bypass, although this group was highly selected - 75% of their cohort had off pump surgery [2]. Our cohort provides some further comparator information quantifying transfusion in this high risk population.

The aim of introducing an organised bleeding management program centred around POCCT was to minimise blood component therapy, whilst maintaining patient outcomes, as recommended by literature and clinical practice guidelines [19-21]. Besides from POCCT, our haemostasis algorithm included calcium management, consideration of transfusion triggers, strong consideration of tranexamic acid, and active warming where possible. We uncovered a large increase in tranexamic acid during the study, but no differences in haemoglobin or calcium could be found.

We significantly reduced our primary outcome, blood transfusion of patients undergoing BSLT on cardiopulmonary bypass, as well as secondary outcomes such as the number of units of each component type. Despite this reduction in blood product use, there was a small decrease in bleeding measured by chest tube drainage early in ICU, and no increase in reoperation or mortality was detected. Although one of our hypotheses was that primary graft dysfunction would be decreased significantly with less blood product use,

there were only small non-statistically significant changes. Primary graft dysfunction is multifactorial, and it is likely that a much larger sample size is needed to detect a change due to the modification of one risk factor. ICU length of stay and ventilation times also remained unchanged, indicating other factors play an important role at our hospital.

Point of care coagulation testing is often considered to be very expensive. Our small cohort showed that in a high risk population the costs of testing were far outweighed by our reduction in blood product cost. The cost of storage, laboratory labour, and of adverse outcomes were not included in this study, and from other studies the real blood product cost is significantly higher than that quoted within this study [22].

The increasing body of literature demonstrating an association of blood transfusion with worse patient outcomes supports implementation of bleeding management strategies in surgery in general, and these should be incorporated into lung transplant programs [5, 7, 23-28]. Our change in bleeding management practice incorporated identifying patients at high risk of bleeding, assessing haemostatic capacity pre-operatively and again on rewarming, and in the bleeding patient.

Rapid results obtained by point of care testing allowed us to use a targeted algorithm based on clinical information rather than ratio driven transfusion. Deficits of hemostasis were diagnosed in detail, and in real-time. Point of care coagulation testing with ROTEM and Multiplate provide specific results regarding intrinsically and extrinsically activated clotting times, platelet and fibrinogen contribution to clot firmness, fibrinolysis and platelet function. Furthermore, results are available with very short turnaround times and streamed live into the operating theatre allowing objective discussion between the surgeons and anesthesiologists regarding bleeding cause and treatment options. While we reduced the incidence of patients requiring most autologous blood products, we noted an increase in patients receiving targeted supplementation of fibrinogen with

cryoprecipitate. Whilst this ended up being non-significant in our small cohort, it mirrored the increase in cryoprecipitate in a similar study in non-transplant surgery at our hospital [15]. Fibrinogen is the coagulation protein with the highest plasma concentration, is essential for hemostasis, and is the first coagulation protein depleted during bleeding and hemodilution [29, 30]. It is therefore expected that in situations of critical bleeding where we used POCCT to rapidly diagnose the cause of bleeding, in many situations fibrinogen deficiency was diagnosed and treated.

Patients on long term immuno-suppression may develop marrow suppression and chronic anemia requiring recurrent transfusions of PRBCs. In the kidney transplant population, this has been associated with prolonged survival, presumably due to TRIM [31]. The evidence is not clear regarding the long term effects of transfusion on acute or chronic lung transplant outcome[18]. However, due to the evidence linking transfusion and poorer outcomes in other settings, we will continue with our bleeding management strategies [24, 28, 32, 33].

While our paradigm shift to targeted, goal directed, bleeding management has resulted in a number of positive outcomes; secondary advantages of a reduction in blood transfusion in small patient cohorts are difficult to quantify. The negative respiratory, circulatory and immuno-modulatory effects of transfusion are likely to adversely affect lung function [6]. Removing this additional insult to a transplanted lung should improve recovery ability, although is not supported by a change in ventilation times and or a statistically significant reduction in ICU length of stay. Furthermore, a reduction in return to theatre for bleeding will reduce infection risk.

Whilst many units do not use cardiopulmonary bypass for BSLT we feel that the results are applicable to all techniques of lung transplantation. It is our unit's belief that the collection of fully anticoagulated blood using cardiotomy and cell saver outweighs the

insult of cardiopulmonary bypass. Off pump and extracorporeal membrane oxygenation supported techniques are widely in use however each has specific drawbacks also. Regardless which method is chosen, conserving the patients' native coagulation ability and red cell mass remain fundamental to patient care.

Furthermore, increasing cost and a decreasing donor pool are becoming significant drivers to implement strategies to reduce transfusion [34-37]. Reducing costs is important in the context of escalating health budgets, out of proportion with economic growth. We have demonstrated significant cost savings over the two time periods with costs per patient decreasing over 60%, an absolute saving of over \$4000 per patient. This has important implications for healthcare institutions as the cost of blood product acquisition, processing and delivery are projected to rise, as well as devolvement of allogeneic blood products costs to individual hospitals [38].

The patient cohorts over the two time periods were similar in both number and pre-operative variables. However, it must be acknowledged that other unknown variables may have had an impact and are beyond our control to manipulate and analyse. These include equipment, other medications, and team experience, the impact of ongoing blood management education and the 'Hawthorne effect' [39]. This is an acknowledged limitation of our study design. Only a randomised controlled trial can eliminate all these variables, but do not generate the "real world" experience this pragmatic study provides.

It must also be acknowledged that evidence for the efficacy of blood transfusion is lacking in many situations despite blood transfusion becoming embedded in medical practice as a 'gold standard' of care. It is also an ethical and moral quandary to conduct RCTs with bleeding patients randomised to 'receive' or 'not receive' transfusion. There is increasing evidence of strong association from observational studies and multifactorial epidemiological analysis (adjusting for confounders) implicating transfusion as a risk for

worse outcomes. It falls to clinicians to make decisions based on the evidence based bleeding management strategies that are available, consider the risk and benefit of any transfusion and avoid assuming transfusion as a default clinical decision.

Conclusion

Our before-and-after cohort analysis in lung transplantation recipients has demonstrated a strong association of reduced transfusion with point of care coagulation testing when used in conjunction with an associated bleeding management algorithm. The reduction in transfusion was achieved with an overall decrease in costs and was associated with a small decrease in early blood loss. We were unable to detect any change in mortality, reoperation, or primary graft dysfunction. POCCT within a bleeding treatment algorithm gives rapid and specific information regarding the cause of bleeding and treatment direction.

Figure Legends

Figure 1. Bleeding Management Treatment Algorithm (Updated),

‘Reprinted from Ref. [15], Copyright (2013) with permission from Elsevier’.

Figure 2. Percentage of Patients Receiving Transfusion Intra and Post Operatively Before and After Change in Bleeding Management Practice

Incidence of patients transfused intra-operatively and postoperatively before and after the implementation of bleeding management. PRBCs (packed red blood cells), FFP (Fresh frozen plasma), platelets, cryo (cryoprecipitate).

Figure 3. Box Plot of Sum Cost

Box Plot of Sum Cost Before and After Change in Bleeding Management Practice

References

1. Cernak B, Verschuuren, E.A.M., Erasmus, M.E., Ismael. F., de Vries, A. J.: **Blood Transfusion Demands in 429 Lung Transplantation Patients Over a 20-year Period in a Single Centre.** *Transfusion Medicine* 2013, **23**(Suppl. 1):21.
2. Wang Y, Kurichi J.E., Blumenthal, N.P. Ahya, V.N., Christie, J.D., Pochettino, A.: **Multiple variables affecting blood usage in lung transplantation.** *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation* 2006, **25**(5):533-538.

3. Triulzi DJ: **Specialized transfusion support for solid organ transplantation.** *Current opinion in hematology* 2002, **9**(6):527-532.
4. Surgenor SD, Kramer RS, Olmstead EM, Ross CS, Sellke FW, Likosky DS, Marrin CA, Helm RE, Jr., Leavitt BJ, Morton JR *et al*: **The association of perioperative red blood cell transfusions and decreased long-term survival after cardiac surgery.** *Anesthesia and analgesia* 2009, **108**(6):1741-1746.
5. Gajic O, Rana, R., Winters, J.L., Yilmaz, M., Mendez J.L, Rickman, O.B.,: **Transfusion-related acute lung injury in the critically ill: prospective nested case-control study.** *American Journal of Respiratory Critical Care Medicine* 2007, **176**(9):886-891.
6. Brun-Buisson C MC, Bertolini G, Brazzi L, Pimentel J, Lewandowski K, et al. : **Epidemiology and outcome of acute lung injury in European intensive care units. Results from the ALIVE study** *Intensive care medicine* 2004, **30**(1):51-61.
7. Weber D, Cottini, S.R., Locher, P., Wenger, U., Stehberger, P.A., Fasshauer, M., Schuepbach R.A., Béchir, M.: **Association of intraoperative transfusion of blood products with mortality in lung transplant recipients.** *Peri Operative Medicine* 2013, **2**(20).
8. Popovsky MA: **Transfusion-associated circulatory overload: the plot thickens.** *Transfusion* 2009, **49**(1):2-4.
9. Christie. J.D. K, R.M., Ahya, V.N., Tino, G., Pochettino, A., Gaughan C., et al. : **The effect of primary graft dysfunction on survival after lung transplantation.** *Am J Respir Crit Care Med* 2005, **171**(11):1312-1316.
10. Diamond JM, Lee, J.C., Kawut, S.M., Shah, R.J., Localio, A.R., Bellamy, S.L.: **Clinical risk factors for primary graft dysfunction after lung transplantation.** *American Journal of Respiratory Critical Care Medicine* 2013, **1**(187):527-534.

11. Tsai AG, Hofmann A, Cabrales P, Intaglietta M: **Perfusion vs. oxygen delivery in transfusion with "fresh" and "old" red blood cells: the experimental evidence.** *Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis* 2010, **43**(1):69-78.
12. Devine DV, Serrano K: **The platelet storage lesion.** *Clinics in laboratory medicine* 2010, **30**(2):475-487.
13. Bui JD DG, Trulock EP, et al. : **Fatal thrombosis after administration of activated prothrombin complex concentrates in a patient supported by extracorporeal membrane oxygenation who had received activated recombinant factor VII. J.** *The Thoracic and cardiovascular surgeon* 2002, **124**:852-854.
14. Hutton B, Joseph L, Fergusson D, Mazer CD, Shapiro S, Tinmouth A: **Risks of harms using antifibrinolytics in cardiac surgery: systematic review and network meta-analysis of randomised and observational studies.** *Bmj* 2012, **345**:e5798.
15. Pearse BL, Smith, I., Faulke, D., Wall, D., Fraser, J. F., Ryan, E. G., Drake, L., Rapchuk, I. L., Tesar, P., Ziegenfuss, M., Fung, Y. L.: **Protocol guided bleeding management improves cardiac surgery patient outcomes.** *Vox sanguinis* 2015, **109**(3):267-279.
16. Weber CF, Gorlinger K, Meininger D, Herrmann E, Bingold T, Moritz A, Cohn LH, Zacharowski K: **Point-of-care testing: a prospective, randomized clinical trial of efficacy in coagulopathic cardiac surgery patients.** *Anesthesiology* 2012, **117**(3):531-547.
17. **What blood products are supplied - national blood product list**
[<https://www.blood.gov.au/national-product-list>]
18. Ong LP, Sachdeva A, Ramesh BC, Muse H, Wallace K, Parry G, Clark SC: **Lung Transplant With Cardiopulmonary Bypass: Impact of Blood Transfusion on**

- Rejection, Function, and Late Mortality.** *The Annals of thoracic surgery* 2016, **101**(2):512-519.
19. **Patient blood management guidelines: Module 2 Perioperative: Australian National Blood Authority** [<http://www.blood.gov.au/pbm-module-2>]
 20. **NICE: Detecting, managing, and monitoring haemostasis: viscoelastometric point of care testing (ROTEM, TEG and Sonoclot systems).** 2014.
 21. 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 *et al*: **2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines.** *Annals Thoracic Surgery* 2011, **91**(3):944-982.
 22. Shander A, Ozawa S, Hofmann A: **Activity-based costs of plasma transfusions in medical and surgical inpatients at a US hospital.** *Vox sanguinis* 2016.
 23. Gombotz H: **Patient Blood Management: A Patient-Orientated Approach to Blood Replacement with the Goal of Reducing Anemia, Blood Loss and the Need for Blood Transfusion in Elective Surgery.** *Transfusion Medicine and Hemotherapy* 2012, **39**(2):67-72.
 24. Ranucci M, Baryshnikova E, Castelveccchio S, Pelissero G, Surgical, Clinical Outcome Research G: **Major bleeding, transfusions, and anemia: the deadly triad of cardiac surgery.** *The Annals of thoracic surgery* 2013, **96**(2):478-485.
 25. Vranken NP, Weerwind PW, Barenbrug PJ, Teerenstra S, Ganushchak YM, Maessen JG: **The role of patient's profile and allogeneic blood transfusion in development of post-cardiac surgery infections: a retrospective study.** *Interactive cardiovascular and thoracic surgery* 2014.

26. Ang LB, Veloria EN, Evanina EY, Smaldone A: **Mediastinitis and blood transfusion in cardiac surgery: a systematic review.** *Heart & lung : the journal of critical care* 2012, **41**(3):255-263.
27. Zacharias A, Habib RH: **Factors predisposing to median sternotomy complications. Deep vs superficial infection.** *Chest* 1996, **110**(5):1173-1178.
28. Karkouti K, Wijesundera DN, Yau TM, Beattie WS, Abdelnaem E, McCluskey SA, Ghannam M, Yeo E, Djaiani G, Karski J: **The independent association of massive blood loss with mortality in cardiac surgery.** *Transfusion* 2004, **44**(10):1453-1462.
29. Levy JH, Welsby I, Goodnough LT: **Fibrinogen as a therapeutic target for bleeding: a review of critical levels and replacement therapy.** *Transfusion* 2014, **54**(5):1389-1405; quiz 1388.
30. Karkouti K, Callum J, Crowther MA, McCluskey SA, Pendergrast J, Tait G, Yau TM, Beattie WS: **The relationship between fibrinogen levels after cardiopulmonary bypass and large volume red cell transfusion in cardiac surgery: an observational study.** *Anesthesia and analgesia* 2013, **117**(1):14-22.
31. Mason DP, Little SG, Nowicki ER, Batizy LH, Murthy SC, McNeill AM, Budev MM, Mehta AC, Pettersson GB, Blackstone EH: **Temporal pattern of transfusion and its relation to rejection after lung transplantation.** *J Heart Lung Transplant* 2009, **28**(6):558-563.
32. Hall TS, Brevetti GR, Skoultchi AJ, Sines JC, Gregory P, Spotnitz AJ: **Re-exploration for hemorrhage following open heart surgery differentiation on the causes of bleeding and the impact on patient outcomes.** *Annals of Thoracic and Cardiovascular Surgery* 2001, **7**(6):352-357.
33. Ariff MH: **Managing bleeding in cardiac surgery.** *ISBT Science Series* 2014, **9**:239–245.

34. Amin M, Fergusson D, Wilson K, Tinmouth A, Aziz A, Coyle D, Hebert P: **The societal unit cost of allogenic red blood cells and red blood cell transfusion in Canada.** *Transfusion* 2004, **44**(10):1479-1486.
35. Christensen MC, Krapf S, Kempel A, von Heymann C: **Costs of excessive postoperative hemorrhage in cardiac surgery.** *The Journal of thoracic and cardiovascular surgery* 2009, **138**(3):687-693.
36. Hofmann A, Ozawa S, Farrugia A, Farmer SL, Shander A: **Economic considerations on transfusion medicine and patient blood management.** *Best practice & research Clinical anaesthesiology* 2013, **27**(1):59-68.
37. Spalding GJ, Hartrumpf M, Sierig T, Oesberg N, Kirschke CG, Albes JM: **Cost reduction of perioperative coagulation management in cardiac surgery: value of "bedside" thrombelastography (ROTEM).** *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery* 2007, **31**(6):1052-1057.
38. Leahy MF, Mukhtar SA: **From blood transfusion to patient blood management: a new paradigm for patient care and cost assessment of blood transfusion practice.** *Internal medicine journal* 2012, **42**(3):332-338.
39. Parsons HM: **What Happened at Hawthorne?: New evidence suggests the Hawthorne effect resulted from operant reinforcement contingencies.** *Science* 1974, **183**(4128):922-932.

	Before Change in Bleeding Management Practice (n=47)	After Change in Bleeding Management Practice (n=46)	P value
Age (years)	43.85 ± 14.09	47.09 ± 12.87	P = 0.318
Male/Female n (%)	25 / 22 (53 / 49)	22 / 24 (48 / 52)	P = 0.680
BMI	22.43 ± 4.44	23.63 ± 4.40	P = 0.135
Cardiac Reoperation/ No Cardiac Reoperation [n (%)]	1 / 46 (2 / 98)	1 / 45 (2 / 98)	P = 1.000
Anaemic/Not Anaemic Males and Females	13 / 34 (28 / 72)	6 / 40 (13 / 87)	P = 0.122
Pre-op Hb	137 (125.5, 148.5)	137 (128, 149.5)	P = 0.580
Preoperative INR	1.14 ± 0.38	1.08 ± 0.33	P = 0.019
Preoperative Creatinine	69.79 ± 19.73	72.39 ± 23.68	P = 0.855
CPB Time (mins)	216.68 ± 56.13	206.41 ± 39.36	P = 0.552
Hb on arrival at ICU	93 (84.4, 102)	93.3 (82.3 (101.3)	0.848
Post-op Calcium levels on arrival at ICU	1.1 (1, 1.15)	1.1 (1, 1.2)	0.056
Reason for transplant [n (%)]			
Bronchiectasis	1 (2.13)	2 (4.35)	P = 0.713
CF	21 (44.68)	17 (36.96)	
COPD	15 (31.91)	13 (28.26)	
IPF	6 (12.76)	10 (21.74)	
OB	0 (0)	1 (2.17)	
GVHD	1 (2.13)	0 (0)	
PAH	1 (2.13)	2 (4.35)	
PAH/COPD	1 (2.13)	0 (0)	
PAM	0 (0)	1 (2.17)	
PLAM	1 (2.13)	0 (0)	

Table 1. are presented as numbers (%), means ± SD, or medians (25th, 75th percentile)

CF cystic fibrosis, COPD chronic obstructive pulmonary disease, IPF interstitial pulmonary fibrosis, OB bronchiolitis obliterans, GVHD graft versus host disease, PAH pulmonary arterial hypertension, PAM pulmonary alveolar microlithiasis, PLAM pulmonary lymphangiomyomatosis

Figure 1

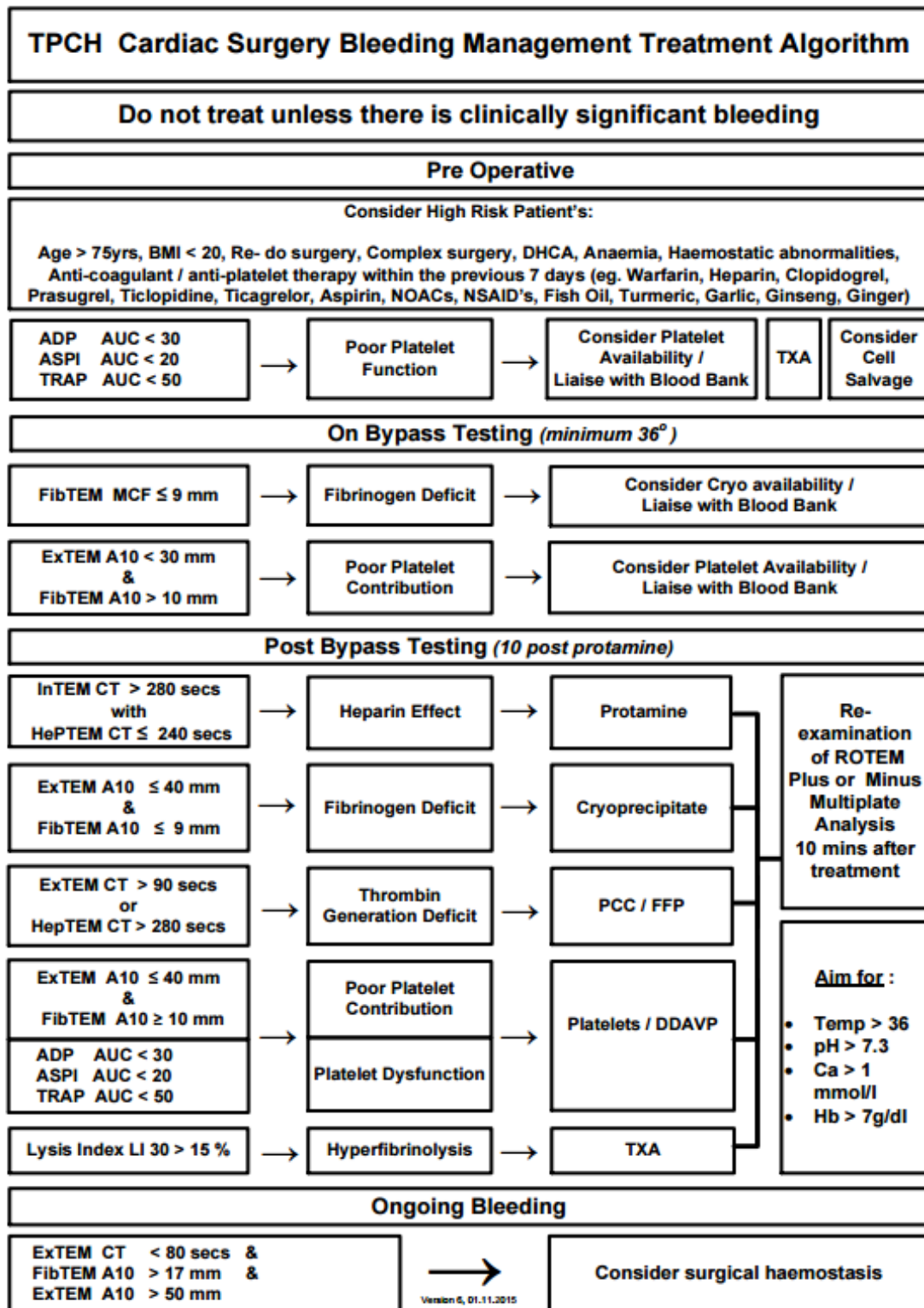


Figure 2

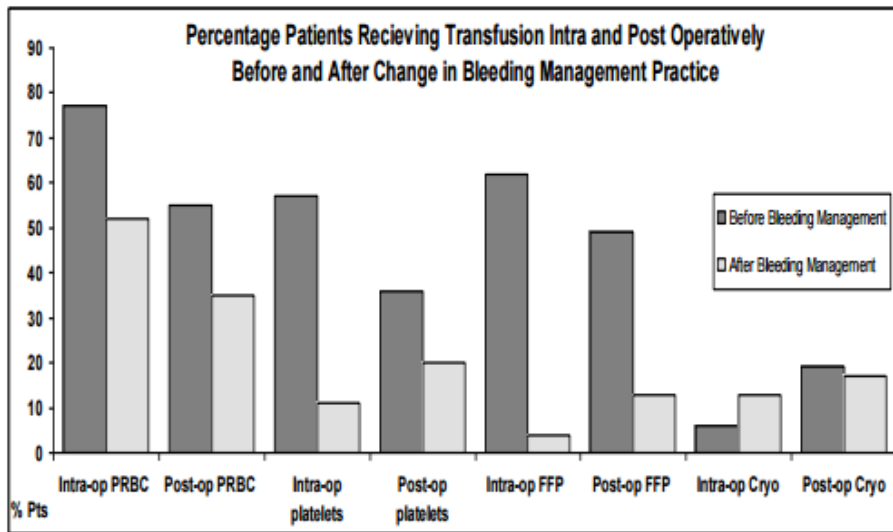


Figure 3

