Complications after Cardiac Surgery due to Allogeneic Blood Transfusions

YM Bilgin1* and LMG van de Watering2
1Department of Hematology, Erasmus MC, Rotterdam-the Netherlands
2Sanquin - LUMC Center for Clinical Transfusion Research, Leiden-the Netherlands

Abstract

Cardiac surgery is worldwide a common procedure, which requires large numbers of red blood cells. Allogeneic blood transfusions are necessary for correction of anemia and bleeding disorders, although blood transfusions are associated with higher morbidity and mortality. Possible complications of blood transfusions contributing to increased risk for morbidity and mortality are transfusion-transmitted infections, transfusion-related acute lung injury (TRALI), and storage of blood products related complications and due to transfusion-related immunomodulation (TRIM). Probably complications due to TRIM are the most common cause of transfusion-related mortality after cardiac surgery. A possible cause for complications due to TRIM is that allogeneic blood transfusions given during cardiac surgery can aggravate a pre-existent inflammatory response after cardiac surgery. In this review we focus on these causes of complications of blood transfusions in cardiac surgery.

Keywords: Blood transfusions; Cardiac surgery; TRALI; TACO; TRIM; Infections; Mortality; SIRS

Introduction

Coronary artery bypass graft (CABG) surgery is frequently performed for re-vascularization of the myocardium. Worldwide approximately 1,000,000 patients are undergoing cardiac surgery annually. Nowadays more older patients with more comorbidities are operated, which is possible due to more advanced techniques. Herewith allogeneic blood transfusions play a crucial role in performing these more complicated surgical procedures. Until the discovery of the ABO-bloodgroups in the early 1900s allogeneic blood transfusions were a high-risk procedure. However the high safety of allogeneic blood transfusions nowadays, there are still risks leading to higher morbidity and mortality associated with allogeneic blood transfusions.

Patients undergoing cardiac surgery consume a large numbers of red blood cells (RBC) transfusions; estimated approximately 20% of the total blood supply [1]. The transfusion rates for CABG show great variability between hospitals with a mean number of transfused units varying between 0.4 to 6.3 units per patient [2]. In this review we will discuss the effects of blood transfusions in cardiac surgery.

Anemia and Blood Transfusions in Cardiac Surgery

Preoperative anemia can be due to several reasons, such as iron-deficiency or gastrointestinal bleeding. The incidence of preoperative anemia in cardiac surgery ranges between 25-32% [3,4]. Several observational studies observed that preoperative anemia was associated with increased neurological and renal complications [5-7]. Anemic patients had a higher risk and late mortality than non-anemic patients undergoing cardiac surgery and not only preoperative anemia also the nadir of the Hemoglobin (Hb) concentration during cardiac surgery is related with worse adverse outcome [8].

During cardiac surgery due to hemostatic abnormalities intra- and postoperative bleeding are commonly seen, which can result in postoperative anemia. In one study up to 44% of the patients had anemia after cardiac surgery [9]. In this study every 1 mg/dL decrease in Hb-concentration was associated with 13% increase in cardiovascular events and 22% increase in all-cause mortality. While massive blood loss is associated with an 8-fold increase in mortality [10].

The main goal of blood transfusions is to increase the oxygen delivery (DO2) to tissues and oxygen utilization by cells (VO2). It has been observed that in cardiac surgery blood transfusions increases DO2 while VO2 remains stable. This is due to enhancement of erythrocyte rheology and thereby improvement of blood physiology as blood viscosity, perfusion and hemodynamic functions.

Although blood transfusions are necessary in cardiac surgery, several studies found that blood transfusions had also deleterious effects. In these studies transfusion of RBCs was dose-dependently associated with postoperative infections and higher mortality [11,12]. In a prospective study in cardiac surgery, 4.8% of patients who did not receive RBCs suffered from postoperative infections, contrasting with 29% in patients who received 6 or more RBC units [13]. In another study patient who received RBC transfusions had a lower heart output and cause more congestive heart failure [14]. These findings suggest that patients with cardiovascular dysfunction have less tolerance to anemia. Besides short-term (30-and 90-days) mortality, also long-term mortality (1-year, 5-and 10-years) was influenced by transfusion of RBCs negatively [15-18]. However all these studies were retrospectively designed and provide by no means proof of a causal role of allogeneic RBC transfusions on postoperative morbidity and mortality. Many factors, such as age and duration of surgery influence the outcome after cardiac surgery. Furthermore sicker and critically ill patients could receive more blood transfusions, therefore no causality between blood transfusions and complications could have proven.

For decades a Hb-level of 10 g/dL was considered as an appropriate trigger for red blood cell (RBC) transfusions. A randomized controlled trial (RCT) performed in the 1990s changed the classical transfusion policy for RBCs drastically [19]; resulting in a tendency for lowering the Hb trigger. In this large RCT in 838 patients, staying at an intensive care unit (ICU), patients were either transfused to maintain the Hb...
value between 7 and 9 g/dl (restrictive) or above 10 g/dl (liberal). Patients assigned to a restrictive trigger received an average of 2.6 units of RBCs compared with 5.6 units in the liberal group. Mortality at 30 days, the primary outcome measure, was not significantly different between the groups: 18.7% versus 23.3% (p = 0.11) in favor of the restrictive trigger arm. In subgroups of patients younger than 55 years of age and those with a lower APACHE (Acute Physiology And Chronic Health Evaluation) risk score, mortality was significantly lower in the restrictive group than in the liberal group: 5.7% versus 13% (p = 0.02) and 8.7% versus 16.1% (p = 0.03), respectively. This study investigated all ICU-patients which represents a heterogenous population. More recent in cardiac surgery one randomized controlled trial suggested that a more restrictive RBC strategy aiming for a hematocrit of 24% is as safe as a liberal RBC strategy aiming for a hematocrit of 30%; the 30-day mortality and severe complications rate was approximately 10% in both groups [20]. However since the implementation of universal leukodepletion of red blood cells in several countries, two observational studies showed that blood transfusions were not associated with higher mortality rates, instead higher Hb concentrations and receipt of blood transfusions were associated with lower hospital mortality [21,22].

Complications of Blood Transfusions During Cardiac Surgery

Several causes could explain for the adverse effects of blood transfusions in cardiac surgery. Most common transfusion-related adverse effects in cardiac surgery are due to transfusion-related acute lung injury (TRALI), blood product storage-related complications and transfusion-related immunomodulation (TRIM).

Transfusion-Related Acute Lung Injury (TRALI) and Transfusion-Associated Cardiac Overload (TACO)

A leading cause of transfusion-associated mortality is transfusion-related acute lung injury (TRALI), which is estimated to occur in general population in about, 1:1,000 to 5,000 blood transfusions and has an estimated mortality rate of 5-10% [23]. In cardiac surgery the incidence of TRALI is higher than in other clinical settings (2.4%) with a mortality rate of 13% [24]. According to an international agreed definition, the onset of TRALI is within 6 hours after blood transfusion [25]. The pathophysiology of TRALI has not been completely clarified [26]. One of the possible causes can be that passively transfused anti-leukocyte antibodies in the donor’s plasma bind to antigens on patient’s neutrophils and initiate priming and activation with release of cytokines, proteases and free oxygen radicals. Neutrophil sequestration in the lungs can finally leading to endothelial damage and capillary leakage. Besides leukocyte antibodies there is circumstantial evidence that other insults such as bio-active lipids accumulating in stored erythrocytes, CD40 ligand in platelet products and cytokines involved in infections can prime neutrophils to adhere to the vascular endothelium [27]. Consequently, TRALI occur more often in patients in whom leukocytes are already primed, such as blood transfusions in the past and immunization by pregnancy. In patients with TRALI who underwent cardiac surgery it has been found that these patients had an already systemic inflammation and activation of neutrophils before blood transfusion, which suggests that blood transfusions act as a second hit in the development of TRALI [28]. This could be the reason that TRALI has a higher incidence in cardiac surgery than in the general population. Transfusion-associated cardiac overload (TACO) refers to pulmonary edema after transfusion of blood products. Recipients with renal or cardiac diseases and older patients are more susceptible for TACO, which is a serious underreported complication of blood transfusions. A retrospective analysis in elderly patients who underwent orthopedic surgery revealed an incidence of 2% after red blood cell transfusions and this could be up to 8% dependent on co-morbidity and age, with a fatality rate varying between 5 to 20% [29]. Due to the cardiac status and more blood transfusions and fluid are given, it is expected that in cardiac surgery the incidence of TACO is higher than in other clinical settings. The discrimination between TACO and transfusion-related acute lung injury (TRALI) can be difficult (Table 1). Patients with TACO have usually more cardiac failure then patients with TRALI [30]. The treatment of TACO consists of volume reduction with eventually ventilatory and/or circulatory support. More important is to prevent the risk of TACO by a restrictive transfusion strategy or the use of diuretics in patients with underlying cardiac and/or renal disease or in elderly patients.

Storage Time of Red Blood Cells

Blood collected from voluntary donors is stored according to the protocols of the blood banks. During storage red blood cells show a number of structural and functional alterations, referred to as storage lesions. Changes in shape, rigidity, depletion of 2,3-diphosphoglycerate (2,3 DPG) and nitric oxide scavenging are presumed to result in impaired perfusion and oxygen delivery [31]. The clinical effects of storage times have only been evaluated in observational studies with unequivocal conclusions in different clinical settings. In cardiac surgery several retrospective studies investigated the storage time of RBCs [32-34], although these studies showed controversial conclusions. More recent an observational study suggests an association between RBCs stored longer than 14 days and postoperative infections [35], while in other two studies no association was found in postoperative length of stay in the hospital, infections and mortality [36,37]. Currently there are RCT’s running, which could answer the questions of storage time of blood products in the future [38].

Transfusion-Related Immunomodulation (TRIM)

Allogeneic RBC transfusions have profound effects on the recipient’s immune system. This immunomodulatory effect of blood transfusions, presumed to result from allogeneic leukocytes are referred to as transfusion-related immunomodulation (TRIM). Compared with other adverse effects, the effects of are excessive [39]. Because allogeneic leukocytes are the most important factor held responsible for the clinical effects of TRIM; RCTs investigating their role are indispensable [40]. To investigate the clinical effects of TRIM several studies were performed comparing leukocyte-containing with leukodepleted blood products in different clinical settings.

Six RCTs are performed in cardiac surgery investigating the effects

| SYMPTOMS                | TRALI                  | TACO                  |
|-------------------------|------------------------|-----------------------|
| Onset of symptoms       | < 6 hours              | Mainly < 6 hours      |
| Respiratory symptoms    | Dyspnea                | Dypnea                |
| Central venous pressure | Normal                 | Increased             |
| Pulmonary wedge pressure| Normal                 | Increased             |
| Fluid balance           | Positive or negative   | Positive              |
| X-ray thorax            | Bilateral infiltrates  | Bilateral infiltrates with signs of fluid overload |
| Echocardiography        | Normal ejection fraction| Decreased ejection fraction |
| B-type natriuretic peptide | Low or normal         | High                  |

Table 1: Possible Differences Between Transfusion Related Acute Lung Injury (TRALI) And Transfusion Associated Cardiac Overload (TACO).
of leukocyte-containing blood transfusions: four of them are published as full articles [41–44]. Two other studies in cardiac surgery are still available only as abstracts, mentioning limited data [45,46]. When the results of RCTs conducted in cardiac surgery are combined in a meta-analysis, the mortality rate was increased with 72% in patients who received leukocyte-containing RBCs (OR = 1.72; 95% CI: 1.05–2.81, p = 0.01) [47]. For postoperative infections the RCT’s revealed different outcomes. Two RCTs showed a transfusion-dose dependent beneficial effect of leukocyte-depleted RBCs [41,43]. Three RCTs did not show benefit of leukocyte-depleted RBCs [42,45,46] and one RCT only in the development of pneumonia [44].

Because in most of Western World universal leukodepletion is implemented, no new randomized controlled trials from these countries are expected. After this implementation several observational studies were performed, comparing the incidence of complications before and after the implementation of leukodepletion. One large multicenter study in critically ill patients from Canada (that included also cardiac surgery patients) reported reduced hospital mortality, decreased occurrence of fever and use of antibiotics after the implementation of universal leukoreduction [48]. Another “before-after study” observed a decrease in postoperative hospital-stay in patients who received leukoreduced blood transfusions [49]. Despite a lot of publications; the controversy on the clinical effects of leukocyte-containing RBCs remains. However there are sufficient data showing that transfusion of leukodepleted red blood cells in cardiac surgery has a beneficial effect.

Inflammatory Response and Blood Transfusions in Cardiac Surgery

During cardiac surgery blood is exposed to the extra-corporeal circuit, ischemia/reperfusion injury and many inflammatory responses are activated. These responses lead to post-perfusion systemic inflammatory response syndrome (SIRS), which can lead to organ failure and infections and subsequently to death. SIRS is defined by a body temperature less than 36°C or more than 38°C, heart rate more than 90/min, tachypnea with breaths more than 20/min or pCO2 less than 4.4 kPa (32 mm Hg) and leukocyte count less than 4x10^9/l or more than 12x10^9/l. SIRS can be diagnosed when two or more criteria are present [50]. SIRS is a subset of cytokine storm with an abnormal regulation of cytokines and is immediately counteracted by a compensatory anti-inflammatory response syndrome (CARS) [51]. An overwhelming SIRS can dominate CARS resulting in multiple-organ dysfunction-syndrome (MODS). While when CARS dominates, this may lead to more enhanced susceptibility for postoperative infections (Figure 1). It has been hypothesized that leukocyte-containing RBC transfusions to patients with an activated inflammatory response (as after cardiac surgery) could further imbalances the postoperative SIRS-CARS equilibrium initially in favour of SIRS; this second-hit response induced by allogeneic leukocytes may be in combination with infections the cause of a more severe MODS [52]. This hypothesis is supported by an observational study, that showed that SIRS was associated with blood transfusions and patients with SIRS had a mortality rate 13-fold higher than in patients without SIRS [53].

The inflammatory response in cardiac surgery is reflected by an increase in several pro- and anti-inflammatory mediators. Several studies investigated the role of allogeneic blood transfusions in relation with inflammatory mediators. One study found in 114 patients who underwent cardiac surgery an association between peri-operative allogeneic RBC transfusions and postoperative increase of concentrations of the inflammatory mediators bactericidal permeability increasing protein (BPI), as a marker of neutrophil activation [54]. While another study found an increase in IL-6 in patients undergoing cardiac surgery who received blood transfusions [55]. Only one study investigated profiles of some inflammatory mediators in relation with leukocyte-containing blood products [56]. In patients who would develop infections, MODS or died had higher pro-inflammatory cytokine concentrations in the group that received leukocyte-containing RBC then in the group that received leukocyte-depleted RBC. These findings of this study support that leukocyte-containing blood transfusions amplify an inflammatory response in addition to an ongoing systemic inflammatory response induced by cardiac surgery.

Conclusions

For correction of anemia and bleeding disorders all blood components are transfused in large amounts in the setting of cardiac surgery. Allogeneic blood transfusions have not only beneficial, but also deleterious effects. Possible causes of complications of blood transfusions in cardiac surgery could be transfusion-related acute lung injury (TRALI), blood product storage-related complications and to transfusion-related immunomodulation (TRIM). Probably complications due to TRIM are the most common causes of transfusion-related mortality after cardiac surgery. It has been suggested that blood transfusions induce a second insult to the systemic inflammatory response that already after cardiac surgery exists. Reduction of the use of blood products in cardiac surgery can further decrease mortality; therefore more research is necessary in this field.

References

1. Snyder-Ramos SA, Möhle P, Weng YS, Böttiger BW, Kulier A, et al. (2008) The ongoing variability in blood transfusion practices in cardiac surgery. Transfusion 48: 1284–1299.
2. Stover EP, Siegel LC, Parks R, Levin J, Body SC, et al. (1998) Variability in transfusion practice for coronary artery bypass surgery persists despite national consensus guidelines: a 24-institution study. Institutions of the Multicenter Study of Perioperative Ischemia Research Group. Anesthesiology 88: 327-333.
3. Elmistekawy E, Rubens F, Hudson C, McDonald B, Ruel M, et al. (2013) Preoperative anaemia is a risk factor for mortality and morbidity following aortic valve surgery. Eur J Cardiothorac Surg.
4. David O, Sinha R, Robinson K, Cardone D (2013) The prevalence of anaemia, hypochromia and microcytosis in preoperative cardiac surgical patients. Anaesth Intensive Care 41: 316-321.

5. Kutler A, Levin J, Moser R, Rumpold-Sellinger G, Tudor IC, et al. (2007) Impact of preoperative anaemia on outcome in patients undergoing coronary artery bypass graft surgery. Circulation 116: 471-479.

6. Karkouti K, Wijeysundera DN, Yau TM, Callum JL, Cheng DC, et al. (2009) Acute kidney injury after cardiac surgery: focus on modifiable risk factors. Circulation 119: 495-502.

7. Zindrou D, Taylor KM, Bagger JP (2002) Preoperative haemoglobin concentration and mortality rate after coronary artery bypass surgery. Lancet 359: 1747-1748.

8. van Straten AH, Soliman Hamad MA, van Zundert AA, Martens EJ, ter Woorst JF, et al. (2011) Effect of duration of red blood cell storage on early and late mortality after CABG. J Thorac Cardiovasc Surg 141: 238-243.

9. Westenbrink BD, Klein L, de Boer RA, Tijssen JG, Warnica WJ, et al. (2011) Sustained postoperative anaemia is associated with an impaired outcome after coronary artery bypass graft surgery: insights from the IMAGINE trial. Heart 97: 1590-1596.

10. Karkouti K, Wijeysundera DN, Yau TM, Beattie WS, Abdelnaem E, et al. (2004) The independent association of massive blood loss with mortality in cardiac surgery. Transfusion 44: 1453-1462.

11. Chelemer SB, Prato BS, Cox PM Jr, O’Connor GT, Morton JR (2002) Association of bacterial infection and red blood cell transfusion after coronary artery bypass surgery. Ann Thorac Surg 73: 136-142.

12. Dixon B, Santamaria JD, Reid D, Collins M, Rechtmter T, et al. (2013) The association of blood transfusion with mortality after cardiac surgery: cause or confounding? (CME). Transfusion 53: 19-27.

13. Koch CG, Li L, Duncan AI, Mihaljevic T, Cosgrove DM, et al. (2006) Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. Crit Care Med 34: 1608-1616.

14. Surgenor SD, DeFoe GR, Fillinger MP, Likosky DS, Groom RC, et al. (2006) Intraoperative red blood cell transfusion during coronary artery bypass graft surgery increases the risk of postoperative low-output heart failure. Circulation 114: 143-148.

15. Koch CG, Li L, Duncan AI, Mihaljevic T, Loop FD, et al. (2006) Transfusion in coronary artery bypass graft surgery is associated with reduced long-term survival. Ann Thorac Surg 81: 1650-1657.

16. Kuduvalli M, Oo AO, Newall N, Grayson AD, Jackson M, et al. (2005) Effect of peri-operative red blood cell transfusion on 30-day and 1-year mortality following coronary artery bypass surgery. Eur J Cardiothorac Surg 27: 592-598.

17. Jakobsen CJ, Ryhammer PK, Tang M, Andreasen JJ, Mortensen PE (2012) Transfusion of blood during cardiac surgery is associated with higher long-term mortality in low-risk patients. Eur J Cardiothorac Surg 42: 114-120.

18. Bhaskar B, Duhunty J, Mullany DV, Fraser JF (2012) Impact of blood product transfusion on short and long-term survival after cardiac surgery: more evidence. Ann Thorac Surg 94: 460-467.

19. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, et al. (1999) A multicenter, controlled, clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 340: 409-417.

20. Hajjar LA, Vincent JL, Galas FR, Nakamura RE, Silva CM, et al. (2010) Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. JAMA 304: 1559-1567.

21. Vincent JL, Sakr Y, Sprung C, Harboe S, Danso P, Sepsis Occurrence in Acutely Ill Patients (SOAP) Investigators (2008) Are blood transfusions associated with greater mortality rates? Results of the Sepsis in the Acutely Ill Patients study. Anesthesiology 108: 31-39.

22. Sakr Y, Lobo S, Knuepek S, Esser E, Bauer M, et al. (2010) Anaemia and blood transfusion in a surgical intensive care unit. Crit Care 14: R92.

23. Webet KE, Blajchman MA (2005) Transfusion-related acute lung injury. Curr Opin Hematol 12: 480-487.

24. Vlaar AP, Hofstra JJ, Determann RM, Veelo DP, Paulus F, et al. (2012) Transfusion-related acute lung injury in cardiac surgery patients is characterized by pulmonary inflammation and coagulopathy: a prospective case-control study. Crit Care Med 40: 2813-2820.

25. Goldmann M, Webert KE, Arnold DM, Freedman J, Hannon J, et al. (2005) Proceedings of a consensus conference: towards an understanding of TRALI. Transfus Med Rev 19: 2-31.

26. Gajic O, Rana R, Mendez JL, Rickman OB, Lymp JF, et al. (2004) Acute lung injury after blood transfusion in mechanically ventilated patients. Transfusion 44: 1468-1474.

27. Silliman CC, Ambruoso DR, Boshkov LK (2005) Transfusion-related acute lung injury. Blood 105: 2266-2273.

28. Vlaar AP, Hofstra JJ, Determann RM, Veelo DP, Paulus F, et al. (2012) Transfusion-related acute lung injury in cardiac surgery patients is characterized by pulmonary inflammation and coagulopathy: a prospective case-control study. Crit Care Med 40: 2813-2820.

29. Popovsky MA, Audet AM, Andrezejewski C Jr (1996) Transfusion-associated circulatory overload in orthopedic surgery patients: a multi-institutional study. Immunohematology 12: 87-99.

30. Skeate RC, Eastlund T (2007) Distinguishing between transfusion related acute lung injury and transfusion associated circulatory overload. Curr Opin Hematol 14: 682-687.

31. Ho J, Sibbald WJ, Chin-Yee IH (2003) Effects of storage on efficacy of red cell transfusion: when is it not safe? Crit Care Med 31: S587-S697.

32. Koch CG, Li L, Sessler DI, Figueueroa P, Hoeltge GA, et al. (2008) Duration of red-cell storage and complications after cardiac surgery. N Engl J Med 358: 1229-1239.

33. Yap CH, Lau L, Krishnaswamy M, Gaskell M, Yli M (2008) Age of transfused red cells and early outcomes after cardiac surgery. Ann Thorac Surg 86: 554-559.

34. van de Watering L, Lorinser J, Versteegh M, Westendornd R, Brand A (2006) Effects of storage time of red blood cell transfusions on the prognosis of coronary artery bypass graft patients. Transfusion 46: 1712-1718.

35. Andreasen JJ, Dethlefsen C, Modrau IS, Baech J, Schonheyder HC, et al. (2011) Storage time of allogeneic red blood cells is associated with risk of severe postoperative infection after coronary artery bypass grafting. Eur J Cardiothorac Surg 39: 328-335.

36. McKenny M, Ryan T, Tsiouris J, Graham B, Young VK, et al. (2011) Age of transfused blood is not associated with increased postoperative adverse outcome after cardiac surgery. Br J Anaesth 106: 643-649.

37. Sanders J, Patel S, Cooper J, Berryman J, Farrar D, et al. (2011) Red blood cell storage is associated with length of stay and renal complications after cardiac surgery. Transfusion 51: 2288-2294.

38. van de Watering LM (2013) Effects of red blood cell storage in heavily transfused patients. Curr Opin Anaesthesiol 26: 204-207.

39. Despotis G, Eby C, Lubin DM (2008) A review of transfusion risks and optimal management of perioperative bleeding with cardiac surgery. Transfusion 48: 26-30.

40. Vamvakas EC, Blajchman MA (2007) Transfusion-related immunomodulation (TRIM): an update. Blood Rev 21: 327-348.

41. van de Watering LM, Hermans J, Houbiers JG, van den Broek PJ, Bouler H, et al. (1998) Beneficial effects of leukocyte-depleted transfused blood on postoperative complications in patients undergoing cardiac surgery: a randomized clinical trial. Circulation 97: 562-568.

42. Wallis JP, Chapman CE, Orr KE, Clark SC, Forty JR (2002) Effect of WBC reduction of transfused RBCs on postoperative infection rates in cardiac surgery. Transfusion 42: 1127-1134.

43. Bilgin YM, van de Watering LM, Eljammal L, Versteegh MI, Brand R, et al. (2004) Double-blind, randomized controlled trial on the effect of leukocyte-depleted erythrocyte transfusions in cardiac valve surgery. Circulation 109: 2755-2760.

44. Connelly CP, Tournopoulou IK, Anagnostopoulos CE, Hillier Z, Rahman FG, et al. (2005) Does leukofiltration reduce pulmonary infections in CABG patients? A prospective, randomized study with early results and mid-term survival. Acta Cardiol 60: 285-293.

45. Bracey AW, Rodavancev R, Nussmeier NA (2002) Leukocyte-depleted blood in open-heart surgery patients: effects on outcome. Transfusion 42: 53.
46. Boshkov LK, Chien G, VanWinkle D, Furnary AP, Wu Y, et al. (2006) Prestorage leukoreduction of transfused packed red cells is associated with significant ongoing 1-12 month survival benefit cardiac surgery patients. Blood 108: 578.

47. Blumberg N, Zhao H, Wang H, Messing S, Heal JM, et al. (2007) The intention-to-treat principle in clinical trials and meta-analyses of leukoreduced blood transfusions in surgical patients. Transfusion 47: 573-581.

48. Hébert PC, Fergusson D, Blajchman MA, Wells GA, Kmetic A, et al. (2003) Clinical outcomes following institution of the Canadian universal leukoreduction program for red blood cell transfusions. JAMA 289: 1941-1949.

49. Fung MK, Rao N, Rice J, Ridenour M, Mook W, et al. (2004) Leukoreduction in the setting of open heart surgery: a prospective cohort-controlled study. Transfusion 44: 30-35.

50. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, et al. (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 101: 1644-1655.

51. Bone RC (1996) Sir Isaac Newton, sepsis, SIRS, and CARS. Crit Care Med 24: 1125-1128.

52. Bilgin YM, van de Watering LM, Brand A (2011) Clinical effects of leukoreduction of blood transfusions. Neth J Med 69: 441-450.

53. Ferraris VA, Ballert EQ, Mahan A (2013) The relationship between intraoperative blood transfusion and postoperative systemic inflammatory response syndrome. Am J Surg 205: 457-465.

54. Fransen E, Maessen J, Dentener M, Senden N, Buurman W (1999) Impact of blood transfusions on inflammatory mediator release in patients undergoing cardiac surgery. Chest 116: 1233-1239.

55. Senay S, Toraman F, Gunaydin S, Kilercek M, Karabulut H, et al. (2009) The impact of allogeneic red cell transfusion and coated bypass circuit on the inflammatory response during cardiopulmonary bypass: a randomized study. Interact Cardiovasc Thorac Surg 8: 93-99.

56. Bilgin YM, van de Watering LM, Versteegh MI, van Oers MH, Brand A (2010) Effects of allogeneic leukocytes in blood transfusions during cardiac surgery on inflammatory mediators and postoperative complications. Crit Care Med 38: 546-552.

This article was originally published in a special issue, Advances in Cardiac Surgery and Therapeutics handled by Editor(s). Dr. Wilbert S. Aronow, New York Medical College, USA