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Cardiac Surgery and Allogeneic Blood Transfusions

Yavuz M. Bilgin
Department of Hematology,
Erasmus Medical Center Rotterdam
The Netherlands

1. Introduction

Coronary artery bypass graft (CABG) surgery is a frequently performed intervention 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 of these more complicated treatments. Until the discovery of the AB0-bloodgroups in the early 1900s allogeneic blood transfusions were a high-risk procedure: more than 50% of the recipients of blood died. The discovery of the blood groups followed by the development of citrate as anticoagulant to prevent clotting of blood enabled the start of safer transfusion medicine. Both World Wars and other disasters in the 20th century had a large impact on further development and structural organization of transfusion medicine. Before the introduction of centrifugation techniques in the 1960s whole blood transfusions were used. Since transfusion of red blood cells, platelet concentrates and plasma became possible over time, treatment of more diseases and opportunities for surgical interventions raised. Nowadays due to stringent donor selection and advanced preparation techniques transfusions of blood components became gradually considered as a safe therapy. From the blood components, red blood cells are used for blood loss and other causes of anemia, while plasma and platelets are transfused to treat or as prophylaxis for bleeding disorders. However unexpected adverse effects leading to more transfusion-related complications are the reasons of serious concerns, which resulted in more evidence-based research aiming to reduce the risks of allogeneic blood transfusions. Nowadays in the Western World every year about 50-70 per 1,000 patients receive a blood transfusion (Cobain et al., 2007), while at the age of 80 years approximately one in five persons has been transfused (Kamper-Jorgensen et al., 2009). Per year 75 millions of blood units are collected and transfused worldwide, thereby yearly saving thousands of lives, facilitating more complex surgery as cardiac surgery and making transfusion of different blood components indispensable for treatment of many diseases. The development of modern transfusion medicine represents one of the greatest achievements of medicine in the 20th century. However the safety of allogeneic blood transfusions is high, there are still risks leading to higher morbidity and mortality associated with blood transfusions. Many clinical and laboratory studies are performed in the past years to decrease the risks of allogeneic blood transfusions.

2. Clinical effects of anemia in cardiac surgery

Anemia is frequently found in patients undergoing cardiac surgery and is associated with postoperative adverse outcome. Cohort studies in patients with cardiovascular diseases, documented that anemia was associated with an increase in mortality. In a large cohort of 78,974 patients older than 65 years with acute myocardial infarction, patients with lower hematocrit (Ht) levels had a higher 30-day mortality rate and red blood cell (RBC) transfusions significantly reduced the mortality rate in patients with a Ht level of less than 30% at admission (Wu et al., 2001). In contrast, a post hoc analysis derived from three large cardiovascular studies showed that patients with an acute coronary syndrome who had received RBCs during the acute phase had (after adjustment for other predictive factors) significant higher 30-day mortality than non-transfused patients (Rao et al, 2004).
In cardiac surgery preoperative as well as postoperative anemia are important prognostic factors for outcome. One study showed that preoperative hemoglobin (Hb) level below 6.2 mmol/l (10.0 g/dl) is associated with higher mortality rate compared to patients with higher Hb values (Kulier et al., 2007). Furthermore, it has been observed that preoperative anemia is associated with increased risk of stroke or kidney failure (Karkouti et al., 2009). The preoperative anemia was also an independent predictor for renal and cerebral complications in patients with a low EuroSCORE; whereas in patients with high EuroSCORE all cardiac and non-cardiac postoperative adverse events were significantly higher in anemic patients. This proves that anemia is less tolerated in patients with higher comorbidities and preoperative anemia should be taken into account in the preoperative preparations (Murphy et al., 2007). Anemic patients had a higher early and late mortality than non-anemic patients undergoing cardiac surgery and not only preoperative anemia also the nadir of the Hb concentration during cardiac surgery is related with worse adverse outcome (van Straten et al., 2009). Furthermore blood loss is a common problem in cardiac surgery, which requires some re-interventions, while massive blood loss (the replacement by transfusion of more than 50 percent of a patient's blood volume) is associated with an 8-fold increase in mortality (Karkouti et al., 2004). These studies in homogenous patient population with high number of blood transfusions show that pre-and postoperative anemia in cardiac surgery are both predictive in early and late mortality.

3. Clinical effects of red blood cell transfusions in cardiac surgery

Due to a more critical oxygen delivery to the myocardium, patients with cardiovascular diseases are less tolerant to anemia than others. Blood transfusions for anemic patients with ischemic heart disease are intended to improve the patient survival. Patients undergoing cardiac surgery consumes a large proportion of RBC transfusions, estimated approximately 20% of the total blood supply (Snyder-Ramos et al., 2008). 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 (Stover et al., 1998). Several observational studies showed that not anemia was associated with increased morbidity and mortality. Also the peroperative administration of RBCs was an important factor associated with mortality and morbidity, which was dose-dependently associated with postoperative infections and higher mortality (Chelemer et al., 2002, Leal-Noval et al., 2001). 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 (Koch et al.,

2006). Also uncomplicated cardiac surgery patients who received preoperative blood transfusions had higher morbidity and mortality (Mohnle et al., 2011). Patients who received RBC transfusions had a lower heart output and cause more congestive heart failure (Surgenor et al., 2006). 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 (Kuduvalli et al., 2005, Engoren et al., 2002, Koch et al., 2006). Especially in patients undergoing combined valve operations with CABG allogeneic blood transfusions played a deleterious role in the long-term outcome. However all these studies in cardiac surgery were retrospectively designed and provide by no means proof of a causal role of allogeneic RBC transfusions on postoperative morbidity and mortality, where many other factors, such as age and duration of surgery influence the outcome. The clinical effects of red blood cell transfusions in cardiac surgery have also been discussed very intensively in several RCTs. We discuss in this chapter the effects of blood transfusions in patients undergoing cardiac surgery. Hereby we focus on studies in cardiac surgery published in the last years that investigated the clinical effects of transfusion triggers of RBCs, storage of RBCs and the immunomodulatory effects of RBC transfusions.

3.1 Effects of transfusion triggers of red blood cells

For decade's a hemoglobin (Hb) level of 10 gr/dl (6.2 mmol/l) 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 (Hebert et al., 1999); resulting in a tendency for lower Hb triggers. 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 favour 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 with different diseases. Recently, in cardiac surgery one randomized controlled trial in 502 patients 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 morbidity was approximately 10% in both groups (Haijar et al., 2010). Several trigger protocols are available developed in the last years aiming to reduce transfusions of RBCs in cardiac surgery. 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 (Vincent et al., 2008 and Sakr et al., 2010). These studies suggest that leukoreduction of RBCs could have beneficial effects. Although, in the last years older patients with more comorbidities are operated, who need more allogeneic blood transfusions. Therefore it seems that sicker patients are undergoing cardiac surgery and they receive more blood transfusions, which make difficult to analyze the exact effects of blood transfusions.

3.2 Effects of storage 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 (Ho et al., 2003). 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 (Vamvakas and Carven, 1999, Yap et al., 2008, van de Watering et al., 2006 and van Straten et al., 2011), although these studies revealed controversial conclusions. Recently an observational study investigated the effects of peri-operatively transfusion of RBCs either stored more or less than 14 days in cardiac surgery (Koch et al., 2008). In this study one-year mortality was higher in patients receiving RBCs stored more than 14 days; however this association between storage time and mortality was only reported as an unadjusted analysis. Identifying confounders were not adjusted for the storage time of RBCs. Factors as publication bias and correction for confounders play an important role in the differences. Also the most associations between storage of red blood cells and outcomes were reported in North-America and none in European countries. This suggests that a difference in blood products and storage conditions between North America and most countries in Europe can cause the intercontinental difference. Recently an observational study from Denmark suggests that there is indeed an association between RBCs stored longer than 14 days and postoperative infections (Andersen et al., 2011). Because different blood products and storage times are used, meta-analysis cannot be used to formulate a reliable consensus on possible associations between storage time of RBCs and morbidity and mortality. Therefore results from prospective, if possible intercontinental, studies have to be awaited.

3.3 Clinical effects of allogeneic leukocytes red blood cells

Allogeneic RBC transfusions have profound effects on the recipient's immune system. This immunomodulatory effect of blood transfusions, presumed to result from allogeneic leukocytes, was recognized in the 1970s of the last century in patients receiving a kidney allograft in which pre-transplant blood transfusions improved the subsequent allograft survival (Opelz et al., 1971). In the 1980s it has been suggested that such immune suppression could enhance cancer recurrence and postoperative infections (Gantt, 1981). These possible adverse effects of blood transfusions are referred to as transfusion-related immunomodulation (TRIM). The existence and possible mechanisms of TRIM are hitherto not understood. Many clinical and laboratory studies investigated the possible immunomodulatory effects and mechanisms of TRIM. Several factors have been suggested to play a role. Most suspected factors are: allogeneic mononuclear cells, soluble biological response modifiers circulating in plasma and leukocyte-derived mediators. Allogeneic leukocytes or soluble factors released by leukocytes during storage have been most extensively studied in the last years (Vamvakas and Blajchman, 2007). Because allogeneic leukocytes are the most important factor held responsible for the clinical effects of TRIM; RCTs investigating their role are indispensable.

Before the 2000s only selected patients received leukodepleted (or leukoreduced) transfusions for the prevention of HLA-allo-immunization, cytomegalo-virus (CMV)-transmission (or reactivation) or febrile non-hemolytic transfusion reactions (FNHTR) due to cytokines or leukocyte antibodies present in the patient. Since 2002 in the Netherlands all

patients who need blood receive leukodepleted blood transfusions. Last years more countries implemented universal leukodepletion for RBCs. If countries that did not convert to universal leukodepletion have to be made a new policy; their decisions should be based on the data of the available RCTs. Or new RCTs should be performed in countries that did not implemented universal leukoreduction to their patients.

To investigate the clinical effects of TRIM several studies were performed comparing leukocyte-containing with leukodepleted blood products in different clinical settings. In cardiac surgery more patients receive allogeneic blood transfusions on average than in other clinical settings. Therefore the role of TRIM in cardiac surgery is important to investigate aiming to understand the effects of allogeneic leukocytes on postoperative complications and outcome.

Six RCTs are performed in cardiac surgery; four of them are published as full articles (van de Watering et al.; 1998, Wallis et al., 2002, Bilgin et al., 2004, Connery et al., 2005). Two other studies in cardiac surgery are still available only as abstracts, mentioning limited data (Bracey et al., 2002 and Boshkov et al., 2006). Two of these trials randomised the patients for three different blood products. The main methods and results are mentioned in Table 1.

From these studies, one study compared buffy-coat-depleted (BCD)-RBCs with two filtered RBCs: fresh filtered RBCs before storage (FF) or stored filtered RBCs (SF) (van de Watering et al., 1998). There was a higher mortality in 60 days (7.8%) in the group who -received BCD-RBCs as compared with 3.6 % and 3.3 % in those receiving FF or SF products respectively ($p=0.015$). This suggests that soluble mediators, still present in the SF products, caused no more adverse effects than FF-RBC, lacking leukocyte-derived soluble factors. In a subgroup analysis, the difference in mortality was present only in patients who received more than three RBC units. A second study (Wallis et al., 2002) using three types of blood products, assigned patients to filtered whole blood (stored < 7 days before filtration), BCD-RBC or plasma-reduced RBCs. Postoperative mortality in 3 months was 0.5%, 2.9 % and 2.5% respectively ($p=0.2$), indicating no additional deleterious role of a higher number of leukocytes present in plasma-reduced RBCs as compared to BCD-RBCs. In the study of van de Watering the incidence of multiple-organ-dysfunction-syndrome (MODS) was not registered, however mortality due to MODS was the major cause of excess deaths after standard BCD-RBC transfusions. Another study was conducted in more complex cardiac valve surgery with a higher probability of multiple RBC transfusions and higher risk for postoperative complications. The aim was to explore the relationship with leukocyte-containing transfusions on MODS and mortality (Bilgin et al., 2004). The primary endpoint (90-day mortality) was (not significantly) reduced approximately with 33% in the patient group receiving leukocyte-depleted RBCs compared with BCD-RBCs (12.7 versus 8.4%, $p=0.16$). And hospital mortality was almost half in the patient group receiving leukocyte-depleted RBCs compared with BCD-RBCs (5.5% versus 10.1%, $p=0.05$). Surprisingly, in this study the incidence of MODS (20%) was similar in the groups receiving standard BCD-RBC or pre-storage filtered RBC; however MODS as a cause of death occurred more often in patients who received BCD-RBC. Subgroup analysis showed that only patients who received more than 3 units suffered higher mortality in the group receiving BCD-RBC (17.6% versus 8.3%, $p=0.02$). A fourth small study in 69 low-risk CABG patients compared bedside-filtered RBCs (containing soluble leukocyte-produced factors) with the same unfiltered RBC product (Connery et al., 2005). There was no difference in mortality between both randomization arms. This study was preliminary stopped because interim analysis showed less respiratory tract infections in the filtered group ($p=0.048$); although the total

Author; year	No. patients (% transfused)	No. RBCs mean ± SD or median	Main endpoints	Results (LD vs BCD)
van de Watering et al.; 1998	914 (95)	FF 5.3 ± 4.1 SF 5.5 ± 5.6 BCD 5.4 ± 5.1	1) Infections 2) 60-day mortality	1) 16.9 vs 17.9 vs 23.0% 2) 3.6 vs 3.3 vs 7.8%[b]
Bracey et al.; 2002 [a]	357 (83)	LD 3 BCD 3	1) Infections 2) Mortality 3) ICU-/Hospital-stay	1) ns; data ND 2) 5.9 vs 7.5% 3) ns; data ND
Wallis et al.; 2002	597 (69)	WBF 3.9 ± 3.9 BCD 3.5 ± 2.6 PR 2.9 ± 1.8	1) Infections 2) 90-day mortality	1) 11.3 vs 10.8 vs 17.7% 2) 0.5 vs 2.9 vs 2.5%
Bilgin et al.; 2004	474 (91)	LD 6.2 ± 7.1 BCD 5.9 ± 6.1	1) Infections 2) MODS 3) Hospital mortality 4) 90-day mortality	1) 22.6 vs 31.6%[b] 2) 20.4 vs 20.7% 3) 5.5 vs 10.1%[b] 4) 8.4 vs 12.7%
Connery et al.; 2005	98 (70)	LD 5.6 ± 13 BCD 5.6 ± 10	1) Infections 2) 30-day mortality	1) 13.2 vs 25.8% 2) 2.6 vs 3.2%
Boshkov et al.; 2006 [a]	1227 (46)	ND	1) Serious infections 2) 60-day mortality	1) ns; data ND 2) 4.9 vs 9.7%

[a] *Published as an abstract*
[b] *Statistically significant ($p \leq 0.05$; compared between leukocyte-depleted and leukocyte-containing RBCs)*
Abbreviations: LD=Leukodepleted RBCs; FF=Fresh filtered RBCs; SF=Stored filtered RBCs; BCD=Buffy-coat depleted RBCs; WBF=White blood cell filtered; PR=Plasma-reduced; ND=Not documented; PTI=Pulmonary tract infections.

Table 1. Summary of RCTs in cardiac surgery investigating the effects of leukocyte-depleted RBCs

infections rate was not different (p=0.22). 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) (37). This difference between both blood products was mainly due to the two studies from the Netherlands (van de Watering et al. 1998 and Bilgin et al. 2004). It should be noted that these large studies were comparable and were conducted in patients with higher risk for postoperative complications and receive larger number of RBC transfusions. Because not all studies are published since their presentation as an abstract, only limited data are present (Boshkov et al., 2004 and Bracey et al., 2002). Therefore some (undocumented) differences in use and preparation of the blood products and in the endpoints could be influenced the differences between the studies.

In cardiac surgery six RCTs were performed investigating postoperative infections, which revealed different outcomes (Table 1). Two RCTs showed a transfusion-dose dependent beneficial effect of leukocyte-depleted RBCs (van de Watering et al., 1998 and Bilgin et al. 2004). Three RCTs did not show benefit of leukocyte-depleted RBCs (Wallis et al, 2002, Bracey et al, 2002, Boshkov et al, 2004) and one RCT only in the development of pneumonia (Connery et al., 2005). The characteristics and main results of these studies in cardiac surgery are mentioned in Table 1. The definitions of postoperative infections are not mentioned in the studies published only as abstracts, although this was not different in the full published studies. These results revealed that patients at risk for high numbers of blood transfusions have a benefit when transfused with leukocyte-depleted RBCs.

The observation that not the soluble mediators released by leukocytes during storage, nor the leukocyte load per transfusion, but rather the number of units transfused that entails the worse outcome, suggests that sicker patients in cardiac surgery requiring more RBC transfusions and are more susceptible to TRIM. We analysed in more detail the causes of death in two RCTs in cardiac surgery from the Netherlands (van de Watering et al., 1998 and Bilgin et al. 2004). This revealed that patients who received standard buffy-coat-poor RBCs, compared with before storage filtered leukodepleted RBCs, excessively died from a combination of infection and MODS (OR 2.92; 95% CI 1.22-6.97; p=0.02). Short-term mortality (60-day) from infections alone and from MODS without infections or from bleeding or surgical complications was equal in both transfusion arms (Bilgin et al., 2007). Although in cardiac surgery the long-term survival is negatively influenced by allogeneic blood transfusions as compared to non-transfused patients (Engoren et al., 2009). The long-term effect of allogeneic leukocytes in RBCs after cardiac surgery is not known and should be investigated in the future studies.

The filtration of the RBC products results in higher costs. However analyses on cost-effectiveness of leukodepletion are scarce and are mainly derived from observational data. In cardiac surgery cost-effectiveness was only analyzed with data derived from the two studies performed in the Netherlands (van de Watering et al., 1998 and Bilgin et al. 2004). The results revealed that leukodepletion of red blood cells have indeed benefits on the total hospital costs. In CABG patients the benefit of leukodepletion of RBCs was between 220-310 US Dollars per life-year gained (Postma et al., 2003) and in cardiac valve surgery on average 214 US Dollars per patient (van Hulst et al., 2005).

Because in most of Western World universal leukodepletion is implemented, no new randomized controlled trials from these countries are expected. Therefore observational studies were performed, that compared the incidence of complications before and after this implementation. 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 (Hebert et al., 2003). Another "before-after study" observed a decrease in postoperative hospital-stay after cardiac surgery in patients who received leukoreduced blood transfusions (Fung et al., 2004). 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 are beneficial in cardiac surgery.

3.4 Laboratory effects of allogeneic leukocytes in cardiac surgery

Cardiac surgery is associated with tissue trauma, ischemia-reperfusion injury and blood surface contact. These conditions induce systemic effects and release of inflammatory

mediators, which are presumed to play a role in the development of postoperative complications such as systemic inflammatory response syndrome (SIRS), multiple-organ-dysfunction-syndrome (MODS) and infections. Moderate SIRS often develops after cardiac surgery and usually resolves with supportive care. However severe SIRS can evolve to MODS, which cause higher morbidity and mortality after cardiac surgery. Shear stress, surface-contact of the CPB and re-oxygenation of the myocardium results in an inflammatory response leading to activation of leukocytes. These responses lead to production and release of several pro-and anti-inflammatory responses during and after cardiac surgery. Imbalance of concentration of cytokines can play a pivotal role in a balanced equilibrium after cardiac surgery. Cytokines are low molecular weight polypeptides, which are produced by many cells, such as macrophages, monocytes, neutrophils and platelets. They are divided into two groups: pro-inflammatory cytokines as interleukin-1 (IL-1), IL-2, IL-8 and IL-12 and anti-inflammatory cytokines as IL-4, IL-5 and IL-10. While IL-6 has both pro-and anti-inflammatory properties. Directly in the postoperative period an anti-inflammatory response is important to further limit the post-surgical inflammatory response.

The production and release of the inflammatory mediators could be predictive in the development of postoperative complications after cardiac surgery. In one study (Sablotzki et al., 1997) the cytokine pattern were measured up to 48 hours after CABG surgery in 24 patients who all recovered uneventfully. After the start of bypass, soluble IL-2 receptor, IL-2 and IL-12 decrease and incompletely restore themselves, respectively 6-48 hours after surgery. The levels of IL-6 and IL-10, undetectable before surgery, increase at the end of bypass and reperfusion. The very high IL-10 peak fades away after 6 hours, while IL-6 remains high up to 48 hours. Such a cytokine pattern shows that cardiac surgery immediately evokes a biphasic cytokine response. Few studies investigated the possible mechanisms of allogeneic leukocyte-containing blood products on the cytokine balance. One a small study in 24 burn trauma patients showed an increase in IL-6 in patients receiving leukocyte-containing RBC transfusions (Nielsen et al., 1999). A larger study found in 114 patients an association after cardiac surgery 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, and IL-6 (Fransen et al., 1999). While another study found an increase in IL-6, but not in TNF-alpha, in patients undergoing cardiac surgery who received blood transfusions (Senay et al., 2009). However none of these studies investigated the combined relationships between the type of blood products, inflammatory mediators and the outcome after cardiac surgery. Therefore the exact effects of blood transfusions in cardiac surgery could not be determined. We were able to investigate profiles of some inflammatory mediators in 346 patients participating in our RCT comparing leukodepekted with leukocyte-containing (buffy-coat depleted) red blood cells. Pre-and post-surgical blood samples were available and the concentrations of inflammatory markers were measured (Bilgin et al., 2010). We selected four key mediators that represent the inflammatory response after surgery. The pro-inflammatory cytokine IL-6 has been shown to be an early predictor for mortality in cardiac surgery. IL-10, an anti-inflammatory cytokine, has been found to be increased after per-operative allogeneic blood transfusions in orthopaedic surgery in association with prolonged hospital stay (Kirkley et al., 1998). IL-12 reflects activation and proliferation of lymphocytes and natural killer cells, which are relevant for the defense against nosocomial infections. The concentration of procalcitonin on the first postoperative day after cardiac

surgery has been shown to be an early marker for organ dysfunction with severe outcome (Falcoz et al., 2005). In patients who would develop infections, MODS or eventually die from these complications had higher pro-inflammatory cytokine concentrations in the group that received leukocyte-containing RBC and lower anti-inflammatory cytokine IL-10 in the group that received leukocyte-depleted RBC (Bilgin et al., 2010). In both study arms the concentration of procalcitonin was not influenced by RBC transfusions. In patients staying longer at ICU the concentration of IL-10 had decreased already on arrival at ICU. The increase of IL-6 and IL-12 peaked later and for IL-6 a higher peak level was measured in the group that received leukocyte-containing RBC than in the group that received leukocyte-depleted RBC. The concentrations of cytokines are shown in Figure 1.

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. This may lead to a more profound counteractive anti-inflammatory response as well to explain enhanced susceptibility for postoperative infections. This inflammatory response can be reduced by transfusion of leukocyte-depleted blood transfusions. One study observed that the cytokine gene expression was altered by transfusion of allogeneic RBCs in patients who developed MODS after cardiac surgery (Sitniakowsky et al., 2011). Furthermore, soluble CD40 ligand which could be accumulated during storage of blood products and could induce the production and release of proinflammatory mediators, was higher in patients who received blood transfusions (Khan et al., 2006). Moreover, recently one study showed higher levels of IL-8, tumor necrosing factor (TNF)-alpha and thrombin-antithrombin-complex (TATc) levels in bronchoalveolar lavage fluid of patients who received perioperative multiple blood transfusions. This study suggests that not only the inflammation system is activated after cardiac surgery, but also the coagulation system is activated (Tuinman et al., 2011). These studies resulted in several hypothesis that investigated the possible relationship between allogeneic (leukocyte-containing) blood transfusions and complications after cardiac surgery.

4. The inflammatory response and allogeneic leukocytes in cardiac surgery

During cardiac surgery blood is exposed to the extra-corporeal circuit, hypothermia, ischemia/reperfusion injury and many inflammatory responses are activated. These responses lead to post-perfusion systemic inflammatory response syndrome (SIRS). SIRS is defined by a body temperature less than 36^0C or more than 38^0C, heart rate more than 90/min, tachypnea with breaths more than 20/min or pCO_2 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 (Bone et al., 1992). 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) (Bone, 1996). An overwhelming SIRS causes a dormant state of cell metabolism, referred to as MODS; SIRS usually resolves with adequate supportive therapy and most of the patients recover. However overwhelming SIRS can dominate CARS and progress to MODS, which may lead to mortality. Previous studies support that leukocyte-containing blood transfusions amplify an inflammatory response in addition to an ongoing systemic inflammatory response induced by cardiac surgery. This may lead to a more profound counteractive anti-inflammatory response as well to explain enhanced susceptibility for postoperative infections. We presume that leukocyte-containing RBC transfusions to patients with an activated inflammatory response (as after cardiac

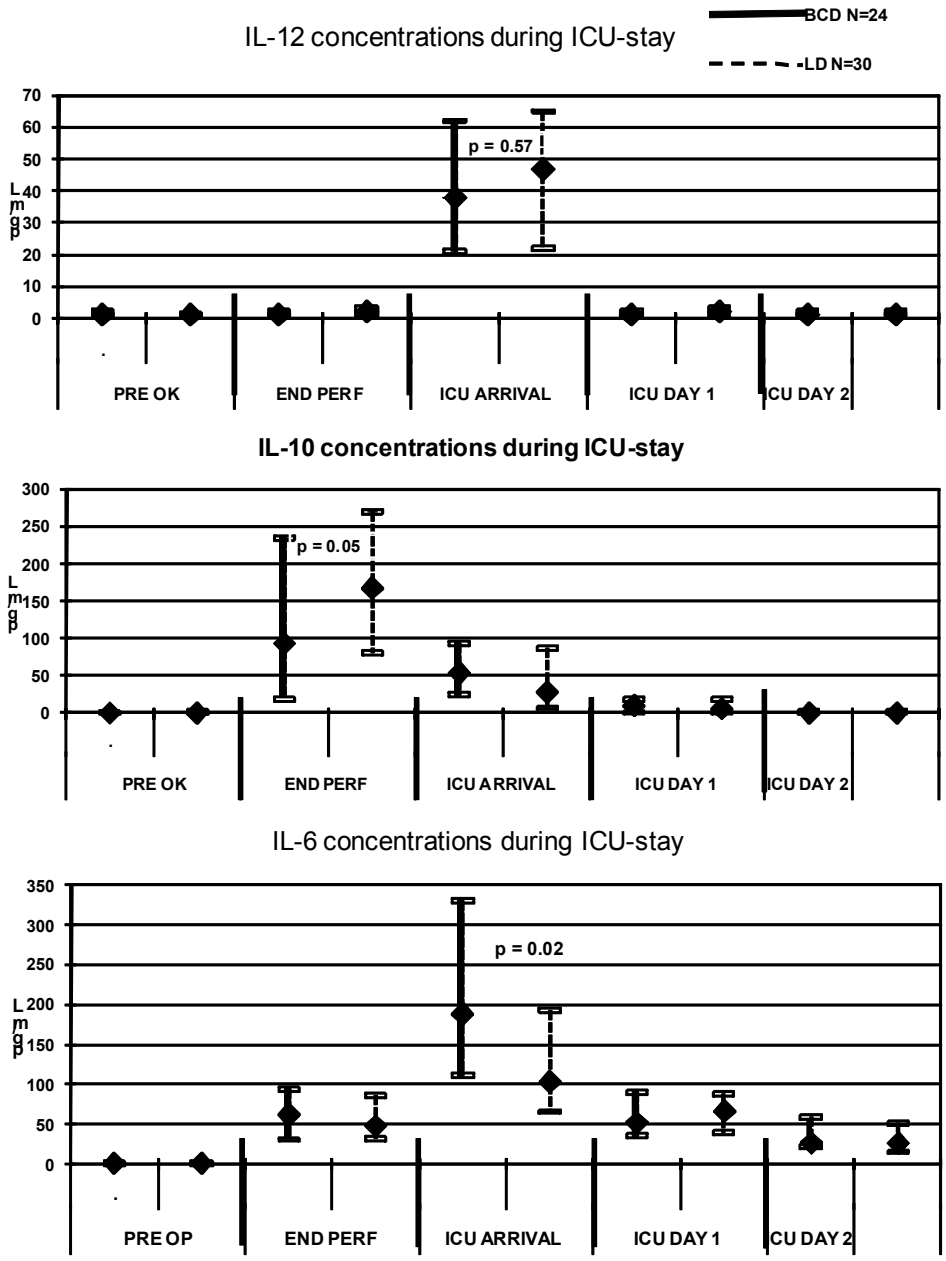

Fig. 1. Pre-operative (PRE OP), at end of perfusion (END PERF), at arrival at ICU (ICU ARRIVAL) and at days 1 and 2 (ICU DAY 1 and 2) the concentrations of cytokines (IL-6, IL-10 and IL-12) (Bilgin et al., 2010).

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 (Bilgin and Brand, 2008). This interaction is shown in Figure 2.

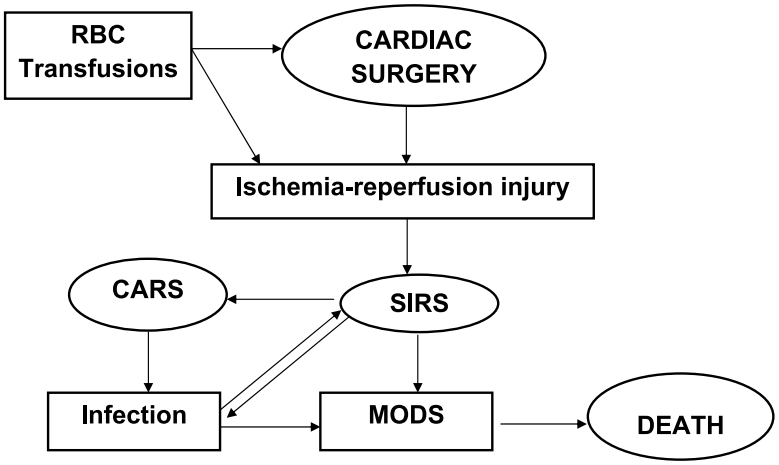

Fig. 2.

This hypothesis initiated a discussion whether allogeneic leukocytes are the substrate for postoperative infections or for MODS. From our RCT we investigated the time-interval in patients who developed MODS and infections in the postoperative period. We found that twice more patients developed MODS after postoperative infections in the group that received leukocyte-containing (buffy-coat depleted) RBCs compared with leukocyte-depleted RBCs. While patients who developed first MODS followed by postoperative infections was comparable in both groups. The difference in deaths between both types of blood products was due to more deaths in patients that developed MODS after postoperative infections and received leukocyte-containing (buffy-coat depleted) RBCs. Deaths in patients with MODS followed by postoperative infections was also not different between both blood products (Figure 3). This suggests that allogeneic blood transfusions initiate first an inflammatory response, which is more pronounced and results more in MODS after transfusion of leukocyte-containing RBCs.

As an explanation for the development of MODS, we found in a laboratory analysis in patients with low mannose-binding lectin (MBL) levels is a risk factor in the development of multiple-organ-dysfunction-syndrome (MODS); when they were transfused with plasma units (Bilgin et al, 2008). The lectin pathway can be triggered by binding of carbohydrates exposed on a wide range of micro-organisms to mannose-binding lectin (MBL) (Neth et al, 2000). Polymorphisms in the MBL gene result in a wide range of functional MBL levels. Roughly 30% of the Caucasian population has reduced levels of MBL, due to single nucleotide polymorphisms in exon 1 of the *MBL2* gene, and approximately 5-10 % has a functional MBL deficiency. MBL deficiency in itself does not lead to clinical problems, but several studies have shown that MBL deficiency confers an increased susceptibility for infections in immune-compromised patients (Bouwman et al, 2005, Peterslund et al., 2001,

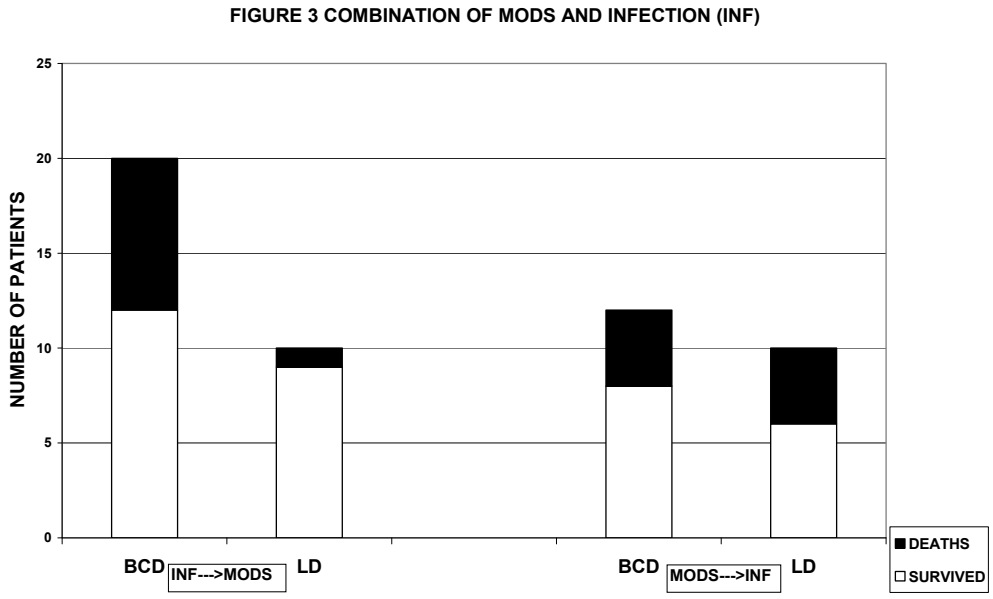

Fig. 3. Relation between allogeneic blood transfusions and MODS combined with infections and survival Abbreviations: LD=Leukodepleted RBCs; BCD=Buffy-coat depleted RBCs

Garred et al., 2003). The role of MBL deficiency on the development and outcome of SIRS and sepsis syndrome is controversial. Worse outcome in patients with sepsis is described (Fidler et al., 2004). Cardiac surgery is associated with MBL consumption, independent of the transfusion of allogeneic leukocytes. We found that patients with MBL-deficiency develop no MODS, unless they have been transfused with FFP, which is associated with MBL reconstitution. Therefore, sustained MBL deficiency may be a favourable status for patients undergoing cardiac surgery (Bilgin et al, 2008). Probably MBL-deficiency plays an protective role in the development of MODS, until patients are transfused with plasma. Furthermore platelet units contain bioactive mediators. Increased CD40 ligand (CD40L or CD154) present in platelet units can induce production and release of pro-inflammatory markers. Besides leukocyte-containing RBCs, plasma and also platelet transfusions could thus aggravate an existing inflammatory reaction impairing the outcome after cardiac surgery. More investigations are needed on the possible causal roles of transfusion of different blood components. Several factors play a role in the inflammatory response after cardiac surgery. One of them is transfusion of allogeneic RBCs, especially leukocyte-containing RBCs. However these factors are not the only one and the exact mechanisms are unravelled until now.

5. Clinical effects of plasma and platelet transfusions in cardiac surgery

Not only RBCs are transfused during cardiac surgery. Patients undergoing cardiac surgery are at increased risk for bleeding, because of thrombocytopenia secondary to hemodilution, platelet dysfunction and consumption of platelets in the extracorporal

circuit. In addition, intra-operatively anticoagulant medication is administered to these patients. To improve hemostasis, platelets and fresh-frozen plasma (FFP) are often transfused in the peri-operative and postoperative periods. Plasma transfusions can contribute to adverse outcome by causing transfusion-related acute lung injury (TRALI), a serious life-threatening condition and an underreported complication of allogeneic blood transfusions. The pathophysiology of TRALI has not been clarified yet, while all plasma-containing blood products could be involved in the development of TRALI (Silliman, 2006). According to an international agreed definition, the onset of TRALI is within 6 hours after blood transfusion. The pathophysiology of TRALI has not been completely clarified yet and is the final result of a cascade of neutrophil priming, activation and endothelial damage. One of the causes is passively transfused anti-leukocyte antibodies in the donor's plasma, which 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 lung is finally leading to endothelial damage and capillary leakage (Silliman et al., 2009). Furthermore it has been suggested that platelet transfusions in cardiac surgery could be associated with postoperative complications. Whether platelet and plasma transfusions contribute to such postoperative complications, or are just a surrogate marker for the need for a higher number of RBC transfusions, is controversial. A predominant role of plasma transfusions on outcome after cardiac surgery is suggested (Ranucci et al., 2008). However other studies that focused on plasma transfusions reported contradictory findings (Banbury et al, 2006 and Sreeram et al, 2005). On the other hand, some studies found that platelet transfusions in cardiac surgery were not been independently associated with mortality (Karkouti et al., 2006 and McGrath et al., 2008), while other studies which applied no correction for concomitant RBC and plasma transfusions (Spiess et al., 2004 and Mangano, 2002). Data from two randomized controlled studies (van de Watering et al., 1998 and Bilgin et al., 2004) were combined to analyze the effects of platelet and/or plasma transfusions on postoperative infections, length of stay in the intensive care unit (ICU), all-cause mortality and mortality in the presence or absence of infections in the postoperative period. This retrospective analysis revealed that the number of transfused plasma units was independently associated with all-cause mortality. Although leukocyte-containing RBCs were associated with mortality, the number of transfused RBC units was not. The number of transfused RBC units, but not the number of transfused plasma units or the receipt of platelet transfusion, was associated with the development of postoperative infections and with the stay in the ICU for 4 or more days. Transfusion of platelet units was associated with mortality with postoperative infections developed during the hospital-stay (Bilgin et al., 2011). Because patients, who receive RBC transfusions, receive also plasma and platelet transfusions, it is difficult to determine whether plasma and platelet transfusions could be independently associated with postoperative complications. This study suggests that plasma transfusions are associated with all-cause mortality, probably by volume overload and transmission of plasma-derived factors. And that platelets and leukocyte-containing RBCs are associated with mortality in the presence of infections, suggesting that both influence the inflammatory response after cardiac surgery. However, only few retrospective studies have considered the effects of plasma and platelet transfusions, which predominantly are transfused to patients who also received RBC transfusions. Our findings underscore the need for further studies to investigate the aggregate effects of all the various blood components transfused in cardiac surgery.

6. Possible relation between blood transfusions and thrombosis

The inflammatory response and pro-inflammatory cytokines also lead to activation of the coagulation system and down-regulate the anticoagulant systems (Levi et al., 2003) Activation of the coagulation factors can in turn activate inflammation. This may enhance the development of infections and microvascular thrombi. Both thrombi and infection play a central role in the development and worse outcome of MODS (Gando, 2010). This could occur by increasing the circulating RBC mass and vascular rheologic deformations by RBC transfusions. Activated platelets (during storage) may contribute to thrombosis in patients at risk. It has recently been shown that leukocyte-containing RBCs and platelets contain prothrombotic soluble mediators, which interact with leukocytes preceding the apoptosis and death of leukocytes, subsequently producing microparticles with procoagulant activity (Keating et al., 2010). Leukocyte-containing RBCs contain prothrombotic soluble mediators, such as CD40L, which induce the synthesis of proinflammatory mediators that can further activate the coagulation system (Blumberg et al., 2006). Observational studies showed an association between allogeneic blood transfusions and the development of venous thromboembolism (Nilsson et al, 2007 and Khorana et al., 2008). The possible association between allogeneic blood transfusions and the formation of thrombosis, as a factor aggravating MODS and having a role in increased mortality due to MODS, is a new subject and should be investigated further. Recently one study found that not only inflammatory mediators were increased in bronchoalveolar lavage fluid after cardiac surgery, also coagulation was activated (Tuinman et al, 2011). This study supports that allogeneic blood transfusions could result in both activation of the inflammatory and coagulation systems.

7. Conclusions

Transfusion of allogeneic blood components is commonly used in cardiac surgery. Several observational and randomized studies found higher morbidity and mortality if patients were transfused with allogeneic blood products. In the last years the clinical effects of transfusion triggers, the storage times and the presence of allogeneic leukocytes in red blood cells were investigated intensively. In cardiac surgery it has been found that allogeneic blood transfusions could increase postoperative complications, which is controversial in the last years. Clinical effects of storage of RBCs are discussed intensively and until now there is no clear evidence that older RBCs are deleterious in cardiac surgery. It has been found that mainly leukocyte-containing blood products play a crucial role in the development of postoperative complications in cardiac surgery. To understand the differences between leukocyte-containing and leukocyte-depleted RBC transfusions we described in this review several possible causal mechanisms. Soluble mediators derived from deteriorating leukocytes during storage of RBC are unlikely to play a role. The complement activation by lectin pathway may be relevant to explore as a causal deleterious effect of plasma transfusions, although does not explain excess death by MODS in association with allogeneic leukocytes. An acute phase reaction represented by procalcitonin could be excluded as a mediator induced by allogeneic leukocytes. A difference in cytokine responses in the recipient was the only significant factor that could be identified as playing a possible causal role. In most countries of the Western World transfusion of leukodepleted blood components is standard practice. Although the final conclusion on this issue is not made yet. Furthermore other factors, such as plasma and platelet transfusions (due to activation or

storage lesions) and the (possible) activation of the coagulation system by the allogeneic blood transfusions, may remain to play important roles in the development of transfusion-associated complications and are input for further improvement of transfusion management in cardiac surgery. Thus many residual questions have still to be answered in the future.

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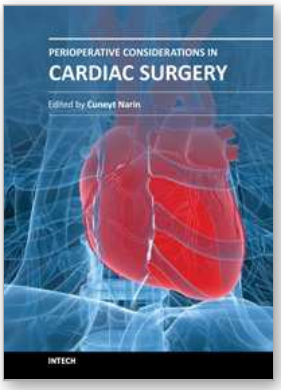

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This book considers mainly the current perioperative care, as well as progresses in new cardiac surgery technologies. Perioperative strategies and new technologies in the field of cardiac surgery will continue to contribute to improvements in postoperative outcomes and enable the cardiac surgical society to optimize surgical procedures. This book should prove to be a useful reference for trainees, senior surgeons and nurses in cardiac surgery, as well as anesthesiologists, perfusionists, and all the related health care workers who are involved in taking care of patients with heart disease which require surgical therapy. I hope these internationally cumulative and diligent efforts will provide patients undergoing cardiac surgery with meticulous perioperative care methods.

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InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
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InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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