

# Hemotherapy in Cardiac Surgery

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## 1. Introduction

Demands for allogeneic blood transfusion in cardiac surgery were still high two decades ago. Today there is a gradual decline in transfusion requirements owing to recent advances in cardiac surgery and related specialties that have together developed techniques for peri-operative blood salvage and its autotransfusion; this trend continues to progress towards bloodless surgery. Its milestones have included a refinement of surgical methods, a better understanding of bleeding pathology related to extracorporeal circulation and an introduction of coagulation monitoring during surgery, using point-of-care testing [1,2,3,4,5]. A significant advancement in extracorporeal circulation came with the development of less aggressive, more biocompatible and miniature-circuit systems [6, 7]. As a result, allogeneic blood transfusion is currently not needed in over 50% of all surgical procedures and in almost 100% of coronary heart operations [8,9]. However, over 40% of patients undergoing cardiac surgery still require allogeneic blood transfusion; of them, 5-7% show an excessive blood loss (more than a normal circulating blood volume), 10-15% have a large blood loss (more than 2000 ml) and about 15-20% have a moderate blood loss (1000 ml to 2000 ml) during the day of surgery up to 7 am next day. The average transfusion requirement ranges between 2 and 4 units of packed red blood cells (PRBC) per adult patient, depending on the centre. Cardiac surgery centers commonly utilize 10 to 15% of the RBCs production of the regional blood bank centers [10].

In the last two decades, the efforts to develop techniques for refinements of surgical methods and peri-operative blood salvage have intensified because of an increase in the number of reoperations and surgery on elderly, polymorbid patients with preoperative anemia. These are the major components of a multi-modality strategy that involves the pre-operative preparation of a patient, surgical procedures, drug administration and homeostatic maintenance (Table 1).

## 2. Autotransfusion

Autotransfusion in cardiac surgery can be divided into three steps according to collection time and the method used, namely, pre-operative autologous blood donation, intra-operative blood collection and post-operative blood salvage.

Modality	Intervention
Preoperative erythrocyte maximizing and/or blood conservation	Fe supplementation, vitamins (C, folates, B12), short-course erythropoietin, Autologous blood donation of 1-3 units: a: blood bank center collection b: perioperative isovolemic hemodilution
Bleeding minimization	Sophisticated technology of incision (argon atmosphere, laser scalpel,...) Refinements of surgical methods Topical hemostatic agents Peroperative blood recuperation Postoperative blood salvage Early revision for surgical bleeding
Hemodilution minimization during CPB	Low priming volume and retrograde priming after starting CPB Ultrafiltration Minicircuits
Homeostasis optimization	Controlled hemostasis ( blood fluidity ) Controlled hemodynamics ( blood pressure ) Normothermia Internal environment (pH, blood gases, ions, glycaemia )
Adherence to basic rule of transfusion	Complying with lowest and safe level of anemia for a given clinical case STS recommended transfusion point: Hb $7 \pm 1$ g/dl .

Table 1. Policy for limitation of blood bank transfusion in cardiac surgery

### 2.1 Pre-operative autologous blood donation

The efficacy of pre-operative blood donation varies according to the time between blood collection and cardiac surgery. The current storage and preservation techniques allow us to collect and maintain 2 to 4 units of full blood or PRBCs. This efficacy can be enhanced by stimulation of erythropoiesis during blood donation, but this is used only selectively because of the potential of thrombotic cardiovascular events and costs [11, 12]. The use of erythropoietin is also limited by the necessity of starting its administration 3 weeks before surgery [13]. A short course erythropoietin was also used several days before cardiac

operation in anemic patients (haemoglobin < 13 g/dl) without autologous predonation [14, 15]. In cardiac patients, there are certain contraindications for participation in autologous blood donation programmes; in addition to anaemia (haematocrit below 33%), they include critical aortic stenosis, idiopathic subaortic stenosis, ischaemic heart disease with unstable angina or with left main coronary artery stenosis, chronic NYHA class IV heart failure, ventricular rhythm disturbances on the day of blood collection and an acute heart attack. This all narrows the selection of candidates for autologous blood donation in cardiac surgery. The proportion of patients meeting the criteria for autotransfusion varies from 10% to 30%; however, some centres can indicate more patients in relation to the range of surgical procedures done and according to experience of the blood collection team.

### **Intra-operative isovolaemic haemodilution**

Blood collection performed immediately before cardiac surgery for the purpose of acute isovolaemic haemodilution is also included in an autologous blood donation programme, thus permitting participation of the patients otherwise contraindicated for a standard programme [16]. A 500- to 1000-ml amount of blood is collected via a central venous catheter or an arterial line and is replaced by a colloid or crystalloid solution before cardiopulmonary bypass (CPB) surgery is commenced. For calculation of the final haematocrit (HCT) value, it is necessary to take the CPB dilutional effect (minimum of 1.3 l) into consideration. Usually, a dilution of 25% to 20 % HCT is used, which is also recommended because of a lower risk of damage to blood elements during extracorporeal perfusion. In some centres, 15% HCT is an accepted transfusion trigger in the patients who do not tolerate allogeneic blood transfusion [17, 18].

The advantage of intra-operative haemodilution is in that the lost blood contains lower red blood cell counts and a transfusion of fresh autologous blood supplies functional platelets. The only contraindication for intra-operative isovolaemic haemodilution is anaemia and haemodynamic instability. Patients with a cardiac disease and a haemoglobin level below 130 g/l may not be able to compensate for a temporary decrease in erythrocyte counts and may show signs of tissue hypoxia or symptoms of cardiac disease. This approach can be combined with blood processing by apheresis.

### **Intra-operative apheresis**

It was first used in thoracic surgery in 1987. It is a medical technology in which the blood of a patient is passed through an apparatus that separates out plasma and platelets and returns the remainder to the circulation. The separated components are then ready for use at the time needed to complete their deficiency. During cardiac surgery with extracorporeal circulation, this technology can also salvage part of the platelets which are otherwise absorbed onto the inner surface of the extracorporeal tubing or can end as platelet-leukocytes micro-aggregates in the capillary beds. The anaesthesiologist can decide between plasma with platelets or a platelet concentrate requiring a slowly rocking shaker for short-term maintenance. Similarly to many blood recuperation devices, the apheresis technique is based on centrifugal force. The proportion of platelets in plasma depends on the spin rate (2400-3600 revolutions per min). The amount of plasma safely collected is related to the patient's clinical condition and usually equals to 20 % of the calculated plasma volume or 12 ml/kg body weight. The procedure design for replenishing intravascular volume, which differs from centre to centre, involves crystalloids and starch derivatives or albumin. When a larger amount of blood is collected, it is necessary to check the ionogram, pH value and free calcium and magnesium

levels. The efficiency of both plasmapheresis and thrombopheresis has been evaluated in many studies. Some have reported lower requirements for allogeneic blood transfusion [19, 20, 21] as well as lower post-operative blood losses [22]. A positive effect of pre-operative plasmapheresis has been demonstrated by low tendency to pathological fibrinolysis [23]. On the other hand, other authors described a low efficacy of pre-operative apheresis in cardiac surgery [24] and related it to the pre-operative administration of an anticoagulation and platelet anti-aggregation therapy. The patients who, before surgery, have received coumarin derivatives, heparin and non-steroidal anti-phlogistic drugs do not benefit from plasmapheresis [25].

## **2.2 Intra-operative blood salvage**

The collection of blood shed from the wound is an integral part of CPB surgery. The procedure consists of two steps, namely, cardiomy suction carried out during CPB with standard heparinisation and blood recuperation during normocoagulation.

### **Cardiotomy suction**

The system is usually composed of two suction lines, two pumps and a cardiotomy reservoir with filters. Blood is retrieved not only from some heart and aorta sections, but also directly from the operative field which continually fills with blood coming from the open sternum and the mediastinum, and from around the cannulae connecting the circuit. The shed blood is aspirated and collected in the reservoir, passes through a filter and is returned via an oxygenator into the circulation. The patient can thus be re-infused with several litres of blood. However, during this process blood is exposed to air in the operative wound and to synthetic surfaces of tubing, which activates a non-specific inflammatory response including coagulation. Suction-produced mechanical stress results in damage to erythrocytes and contributes to haemolysis. An improvement could be achieved by processing shed mediastinal blood in an autotransfusion device that would separate viable erythrocytes from the rest of activated blood with cellular detritus, fat and vasoactive mediators. A good effect on pulmonary function and haemodynamics has been shown in patients receiving processed blood [26]. This technique, however, is not much used because of technical problems with processing large volumes of blood and the necessity of plasma and platelet substitution.

### **Blood recuperation**

The processing of blood drained from the operative wound is carried out at the time the patient is not fully heparinised, i.e., before the beginning or after the end of extracorporeal perfusion. If, after the termination of perfusion, a large volume of blood with low HCT is left in the reservoir, its recuperation is advisable, particularly when problems with renal function are expected. A large reservoir blood volume can be avoided by inserting a haemofiltration coil in the CPB system. The approach, however, removes only water and low-molecular-weight substances.

From the clinical point of view, the patient always benefits from blood recuperation because no or only few blood products are necessary [27]. In terms of costs, the situation depends on the degree of bleeding. With current blood products prices on the one hand and the costs of a recuperation set on the other, the results are equal if at least two PRBC units are obtained. It means that recuperation is cost-effective in patients with excessive

blood loss; the costs of both approaches are equal in patients with large blood loss and, in patients with low blood loss, recuperation comes at an increased cost to the institution [28]. This medico-economic analysis would be right on the assumption that transfusion of allogeneic PRBCs is as valuable as fresh autologous blood transfusion. The present-day evidence suggests that this is not true, although the major risks of allogeneic blood transfusion, such as infection or immunomodulation, are minimal. Packed red blood cells are more suitable for correcting severe chronic anaemia than for an acute large blood loss. Transfused banked erythrocytes are not capable of immediate oxygen release for tissue supply, and their accumulation in the pulmonary vascular bed may do acute damage to the lung tissue, causing right-sided pulmonary failure and paradoxically making circulatory shock worse. Nonetheless, for a patient with excessive blood loss, allogeneic blood transfusion is the only possible choice. Because of increasing awareness of these facts, blood recuperation is becoming a routine method in a growing number of centres for cardiac surgery and is currently used in about 50% and 60 % of these institutions in the EU and North America, respectively.

### **2.3 Post-operative blood salvage**

The method of collection and re-infusion of mediastinal blood shed during surgery and drained in the early post-operative period has been used in cardiac surgery since 1978 [29]. The blood is collected into a special auto-transfusion device, or the cardiectomy reservoir of a CPB system can be used when it is connected to mediastinal drainage and a vacuum generator and with anti-coagulation citrate solution added. The cardiectomy reservoir involves a 40- $\mu$  filter, but insertion of an additional 20- $\mu$  filter in the outlet line is recommended. The salvaged blood has 20-25% HCT, a small number of platelets, free haemoglobin and no fibrinogen. It also contains fibrin-degradation products, cardiac enzymes and other inflammatory factors which may adversely affect biochemical tests and clinical outcomes [30, 31]. In spite of the disadvantages, this is a safe technique which can reduce demands for blood transfusion particularly in patients with blood loss exceeding 500 ml in the first two hours [32]. Doubts concerning the quality of salvaged erythrocytes were challenged by Schmidt et al. who did not find any differences in survival between the red blood cells of shed mediastinal blood and those of circulating blood [33]. At present the use of a recuperation technique for mediastinal blood is preferred because it reduces the organism's burden by free haemoglobin and inflammation mediators [34]. It is usually carried out in continuation of intra-operative recuperation and is regarded as a safe method up to 8 hours of the patient's transfer to an intensive care unit [35].

## **3. Blood bank products**

A rational therapy with blood products and derivatives requires that their administration be based on a documented deficiency or dysfunction. However, surgical bleeding may be associated with additional haemostatic risk factors. A prolonged hypovolaemia with subsequent shock can initiate consumption coagulopathy and the substitution with crystalloids and colloids will result in clotting factor dilution. With the exception of patients with serious vascular disease or very old persons, the majority of patients can tolerate anaemia with a haemoglobin concentration of 7 g/dl or 24% HCT. However, in

the early phase of circulatory and haemostatic homeostasis, it is advisable to increase Hb concentration to 8g/dl in order to spare the compensatory capacity of myocardium (increased cardiac output) and to utilise a possibility to regulate systemic blood pressure by blood viscosity. In patients with serious peripheral arterial disease, it is reasonable to increase the transfusion trigger. Transfusion should be administered only after the patient's medical history and their actual health status have been taken into consideration [36, 37].

### 3.1 Allogenic blood transfusion

In cardiac surgery, blood transfusion is indicated to correct severe anaemia due to excessive bleeding caused by vessel disruption during surgical exposure and dissection or by coagulopathy. Severe anaemia is characterised by a decrease in Hb concentration which leads to diffuse or localised tissue ischaemia. The attitudes to indications for transfusion have developed under the influence of diverse subjective views, ranging from a miraculous remedy to an absolute refusal, as well as on evidence-based information. Patients can greatly benefit from blood transfusion, if it is life-saving, or be severely harmed if a serious infection is transferred. The risk of viral infection transfer has recently decreased so much (HIV or HCV transfer is one per million transfusions) that it should no longer be a limiting factor in blood transfusion [37].

Transfusion can also induce immunomodulation in the recipient, i.e., stimulation or inhibition of immune responses. The former involves the production of antibodies (alloimmunisation) against the surface antigens including HLA, which has several adverse effects. The latter, immune depression, involves a decrease in the ratio of circulating T-lymphocyte subpopulations (CD4+/CD8+) and impaired function of natural killer cells and antibody production by lymphocytes. The development of immunomodulation is associated with donor leukocytes; their removal can by half reduce the incidence of adverse conditions, such as transfusion-related acute lung injury (TRALI) [38]. In addition, immunomodulation can enhance susceptibility to infection, as suggested by a strong association found between transfusion and post-operative infection in a retrospective study on 15 000 patients surgically treated for ischaemic heart disease in Cleveland in 2006 [39].

Blood transfusion offers three advantages: it increases blood oxygen-carrying capacity, provides volume to support cardiac output and improves homeostasis; however, only the first one is the indication criterion. Which situation, therefore, requires an increase in oxygen-binding capacity of the blood by means of transfusion? A defined threshold Hb concentration is not the answer, because the capacity of blood to transport oxygen depends on other parameters such as cardiac output, pulmonary oxygenation, and haemoglobin ability to bind and release oxygen. Nevertheless, based on studies and expert opinions, a consensus has been reached that transfusion is beneficial to patients with an Hb concentration below 7 g/dl while it brings no benefits to patients with an Hb level above 10 g/dl. Moreover, an increase in oxygen-carrying capacity by transfusion is not accompanied by an immediate increase in oxygen delivery to tissues, because stored erythrocytes are depleted of 2, 3-diphosphoglycerate and nitric oxide concentrations, which markedly reduces their ability to offload oxygen. To recover this ability takes several hours, and blood bank transfusion thus only adds to haemodilution of functional haemoglobin and a transient drop in oxygen supply.

In healthy individuals, an acute anaemic state no longer manageable by compensatory mechanisms and leading to a switch to anaerobic metabolism occurs at Hb levels between 3 and 4 g/dl. This is associated with venous haemoglobin oxygen saturation of 56%, which equals to a tissue supply of 333 ml oxygen/min/m<sup>2</sup>. The major compensatory mechanisms include increased cardiac output, an increase in oxygen extraction and an increase in capillary erythrocyte transit time. Patients with coronary heart disease may develop acute anaemia at an Hb level of about 6 g/dl. These limit values have been obtained in animal experiments and confirmed by cardiac surgery in several thousands of Jehovah's Witness patients. The level of evidence, defined as C and D, allows us to accept the fact that, in certain clinical situations, patients can tolerate an Hb concentration of about 6 g/dl. The range of clinical conditions is very broad and, in the present-day ageing polymorbid population, there are not many patients who would tolerate acute anaemia with threshold Hb values 6 g/dl.

### 3.2 Fresh frozen plasma (FFP)

Full blood collected from donors is treated by plasmapheresis or centrifugation to obtain plasma which is frozen within 6 hours of collection. Although FFP is indicated for documented either isolated or multiple coagulation factor deficiencies (II, V, VII, IX, X, XII), it has formerly been used as volume replacement and in the prophylaxis of potential coagulopathy in relation to massive transfusions and extracorporeal circulation. At the 1984 conference on FFP it was concluded that such indications for FFP administration are not justified and this conclusion has so far been accepted [40,10]. Prophylactic FFP administration on the basis of massive transfusion (more than 10 red blood cell mass units) and abnormal laboratory tests (PT and aPTT) in the absence of clinically apparent bleeding is not supported by evidence either. Abnormal PT and aPTT results are often found even after five administrations of blood transfusion. Their positive predictive value is only about 30%. However, patients in whom the blood transfusion volume exceeds the total blood volume will always require either platelet substitution or FFP, or both products. A correlation between the volume of lost plus transfusion blood and the occurrence of coagulopathy is not a simple one. On the other hand, there is a strong correlation between the occurrence of coagulopathy and the duration of hypotension and/or hypothermia. Patients with no or only a short period of hypotension, even if they receive massive transfusion, will not have coagulopathy while those exposed to one hour of hypotension will often develop a serious form of it. Similarly, hypothermia plays an important role; its avoidance is a decisive factor in the prevention of coagulopathy after massive transfusion. Patients undergoing cardiac surgery with extracorporeal circulation experience a drop in coagulation factor levels by 30 to 40 %, but only few of them show clinical bleeding. Excessive bleeding after cardiac surgery, if not due to surgical reasons, results from platelet dysfunction or their deficiency, and/or is caused by hypothermia, prolonged hypotension (circulatory shock) or residual heparinisation. Because of the lack of scientific evidence for clinical efficacy, indication criteria for the use of FFP are largely based on cardiac surgeons' expertise. They include: 1) substitution therapy in isolated or multiple coagulation factor deficiencies.; 2) need to reverse over-warfarinisation, in that case two units are administered in the non-bleeding patient and six units in the bleeding one; 3) treatment of pathological bleeding due to a transfusion volume being larger than the patient's total blood volume.

### 3.3 Thrombocyte concentrate (TC)

Thrombocyte concentrates are transfusion products obtained from full blood by centrifugation. A pooled-donor TC is derived from four to six blood donors to give one therapeutic thrombocyte transfusion unit for an adult patient. A single-donor TC is obtained by apheresis using a platelet separator. Both products contain over  $200 \times 10^9$  platelets in a 250- to 350-ml plasma volume. The TCs are stored in special storage bags allowing gas exchange on a shaking apparatus at 20-24°C for up to 5 days. In TC infusion, the ABO-blood group/Rhesus factor of the patient must be respected. If a TC of the required blood group is not available, thrombocytes suspended in plasma ABO compatible with the recipient's erythrocytes can be administered. Other options include a TC from an O-blood group donor who has a low titre of anti-A and anti-B agglutinins or the use of platelets resuspended in a plasma substitute. An Rh-positive donor can receive a TC from an Rh-negative donor, but not vice versa [41].

In major surgical procedures, it is recommended to maintain the platelet count above  $50 \times 10^9/l$  because of a risk for microvascular bleeding. In cardiac surgery with cardiopulmonary bypass, where platelet-related defects are the most frequent cause of haemostatic abnormality, the recommended platelet count is 50-100  $\times 10^9/l$  [42]. An increase above this level is justified only in severe platelet dysfunction. Platelet concentrates should not be administered routinely in cardiac surgery because it has been associated with increase in multi-organ failure and death [43, 44]. One therapeutic TC unit in an adult patient increases the platelet count by 10-20  $\times 10^9/l$ . The therapeutic efficacy is assessed by clinical signs (decrease of bleeding) or laboratory evidence of increased platelet counts.

An insufficient increase in platelet counts can be due to reasons such as low TC quality or higher requirements for platelet counts in patients with trauma or disseminated intravascular coagulation. However, the most serious cause involves immune destruction of platelets by alloantibodies or autoantibodies, and this is suspected when other causes are excluded.

## 4. Blood bank transfusion for urgent procedures

In transfusion practice safety requires that allogeneic blood be cross-matched with the recipient's blood; the test takes about 60 min. In emergency live-saving procedures or unexpected massive blood losses, it is possible to perform transfusion after a minor cross-match test or without it, or to administer ABO/Rh compatible blood or O-type blood.

If immediate transfusion is necessary and the recipient's blood group is not known, then it is justified to use uncrossmatched type-O packed red blood cells (UORBC) that lack A and B surface antigens. For potential expecting mothers, the UORBCs should always be Rh negative to avoid sensibilisation and damage to the foetus in case the mother is Rh-negative. The patients should be given no more than 10 UORBC units and subsequently receive transfusion with standard blood testing.

If there is time to do blood group testing, ABO-compatible PRBCs are administered without a cross-match test.

In about 3 % of the human population, serum contains anti-erythrocyte antibodies which in a great majority (85 %) are of one type only. The magnitude of risk for a post-transfusion reaction is equal to this frequency, but the results from trauma centres show that it is in fact

even lower. Gervin et al. have recorded no reaction in 875 transfusions without cross-matching in 160 patients [45].

When more time is available (about 20 min), a minor cross-match test is done which reveals most of the donor uncommon anti-erythrocyte antibodies. It fails to detect abnormal antibodies in only 0.04% of the patients and this makes the probability of post-transfusion reaction extremely low.

It can be concluded that, seen in a historical perspective, the needs for blood transfusion in cardiac surgery have varied, but are still high. With advances in cardiac surgery during the last 50 years, a significant decrease was recorded in the average blood product requirement per patient, but this trend has recently had declining tendency. The reason lies in increasing numbers of reoperations and surgery on very old and polymorbid patients with preoperative anemia. Our conclusion suggests a multi-modality blood-saving strategy ranging from patient pre-operative preparation, over surgical and autotransfusion techniques and drug intervention to homeostatic maintenance. So far this strategy has brought about results in the form of an increasing number of operations not requiring transfusion; this is currently more than 50 % of all cardiac surgery procedures. Despite its risks, allogenic blood transfusion still remains an important supportive and life-saving measure in ultimate situations.

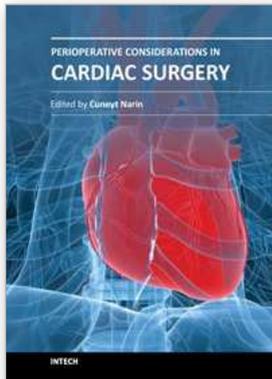
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## **Perioperative Considerations in Cardiac Surgery**

Edited by Prof. Cuneyt Narin

ISBN 978-953-51-0147-5

Hard cover, 378 pages

**Publisher** InTech

**Published online** 29, February, 2012

**Published in print edition** February, 2012

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.

### **How to reference**

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Robert Wagner (2012). Hemotherapy in Cardiac Surgery, Perioperative Considerations in Cardiac Surgery, Prof. Cuneyt Narin (Ed.), ISBN: 978-953-51-0147-5, InTech, Available from:

<http://www.intechopen.com/books/perioperative-considerations-in-cardiac-surgery/hemotherapy-in-cardiac-surgery>

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