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The role of cell savers and filters in cardiac surgery

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Chapter 1

General introduction

General introduction

Although there is widespread and increasing evidence for a lower threshold in transfusion of red blood cells, transfusions are still common in patients undergoing cardiac surgery and continue to increase¹⁻³. The transfusion threshold has been steadily decreasing the past decades, but up to the beginning of 2015 no high quality study and no international consensus on the optimal haemoglobin concentration at which to transfuse in the cardiac surgical population exists⁴⁻⁸. Recently a high quality study was published that showed that a restrictive transfusion threshold was not superior to a liberal transfusion threshold⁹. In the peri-operative care for cardiac surgical patients, transfusion guidelines are formed on a national or local level, but personal physician beliefs still play a large role in a significant proportion of the prescribed transfusions¹⁰. Thus, transfusion thresholds vary widely between physicians, hospitals and countries^{11,12}.

There is ample evidence, mainly based on physiological findings, for the use of red blood cell transfusions to improve oxygen delivery to tissues in states of haemorrhage and/or anaemia^{1,2,4,5}. The WHO defines anaemia as a hemoglobin (Hb) concentration below 8.1 mmol/l for men and below 7.4 mmol/l for women. Its presence is associated with increased intensive care and hospital length of stay and increased mortality in cardiac surgery^{13,14}. Intra-operative anaemia may be the cause of post-operative kidney injury requiring renal replacement therapy and it is also associated with a prolonged intensive care unit stay and a higher mortality rate¹⁵.

The negative effects of blood transfusions are on the other hand well known. Blood transfusions have been described to increase morbidity and mortality in patients undergoing or after cardiac surgery¹⁶⁻²⁰. Transfusion of blood and blood products may cause lung injury, increase the incidence of post-operative pneumonia, and prolong post-operative mechanical ventilation and thus the length of intensive care stay^{16,18,21,22}. Furthermore, allogeneic blood transfusions are associated with increased post-operative infections, including sternal wound infections and sepsis^{23,24}. Sternal wound infections in turn have a strong association with the number of re-thoracotomies and persistent bleeding is a common cause for a re-thoracotomy. In light of this evidence, a reduction of peri-operative blood transfusion is desirable and important for both patient and the health care provider.

Blood transfusion sparing strategies

Not surprisingly, a lot of effort has been put in means to decrease the number of red blood transfusions in cardiac surgery by publishing multi-disciplinary guidelines for clinical practice in blood sparing strategies. These can generally be divided in to pre-, intra- and post-operative strategies ^{1,2,25-28}.

Pre-operative blood conservation strategies include patient risk assessment, management of drugs that interfere with coagulation (i.e. cessation of acetylsalicylic acid, P2Y₁₂ ADP receptor blockers, coumarins), adequate diagnosis and therapy of pre-operative anaemia.

Intra-operative blood conservation strategies can be divided into pharmacological interventions (i.e. the use of anti-fibrinolytic and pro-haemostatic drugs), the prevention of haemodilution (i.e. a restrictive fluid management), adequate monitoring of blood coagulation and the application of restrictive transfusion triggers. Further actions can be taken while the patient is on cardiopulmonary bypass (CPB) (i.e. use of biocompatible coatings, performing off-pump surgery, maintaining normothermia) and the use of cardiotomy suction and/or cell savers. Post-operative blood conservation strategies are essentially the same as the intra-operative strategies, including the use of cell savers.

Although much effort has been put into providing physicians with evidence-based guidelines on blood sparing strategies, there is still much debate about the efficacy of many of these recommendations ³. This is mainly because the levels of evidence on which guidelines are based are often low and large randomized controlled clinical trials have not been performed yet. In addition, there is a plethora of small studies on blood sparing strategies with different and sometimes contradicting results. Unfortunately there is also the difficulty in changing longstanding transfusion practices, a "low and slow adoption rate", on the practitioners level ^{3,10}. Without strong evidence changing clinical practice and personal attitudes is difficult.

Focus on cardiotomy as blood sparing strategy

As mentioned cardiotomy suction can be used as a strategy to reduce blood loss during cardiac surgery and hence reduce the need for allogeneic blood transfusions. The cardiotomy suction was introduced in the 1960s as an extension of the intra-

cardiac vent. During CPB blood from the surgical field together with other contents of the pericardial cavity, is aspirated into a cardiomy reservoir. After passing through the oxygenator the blood is returned to the patient instead of discarding it. Although this strategy is considered standard practice in cardiac on-pump surgery and its use is especially justified in the presence of rapid significant blood loss there is surprising little to no evidence for cardiomy suction use during CPB in routine cardiac surgery as a blood conserving strategy ^{2,29}.

Cardiomy blood quality

Besides the lack of evidence for the use of cardiomy suction in routine cardiac surgical procedures, there are also disadvantages with the use of cardiomy suction. The cardiomy blood differs markedly from intravascular blood or blood within a closed CPB circuit with respect to altered coagulation, induction of inflammation, formation of micro-particles and induction of haemolysis.

Exposure of the shed blood to tissue factor results in activation of the coagulation system with release of thrombin and fibrin. In addition, tissue plasminogen activator released from the surgical trauma stimulates fibrinolysis. Analysis of pericardial shed blood shows high concentrations of markers of both clotting activation and fibrinolysis. Furthermore platelets are activated during extravasation of blood into the pericardial cavity. This results in aggregation, degranulation and consumption of platelets, as well as the release of inflammatory markers (for example interleukin-6). ³⁰⁻³³. Activation of the coagulation cascade inevitably results in co-activation of inflammatory cascades ^{29,34}. As a consequence, pericardial suction blood contains high concentration of pro-inflammatory cytokines and as such retransfusion of cardiomy blood may contribute to the inflammatory response associated with cardiac surgery and can impair haemodynamics, renal and pulmonary function ^{29-31,35-37}.

The pericardial space also contains a mixture of organic and non-organic debris such as sternal marrowfat, aggregated platelets and fragments of bone wax. Furthermore, there is mixing of air and blood with subsequent formation of micro-particles when blood is aspirated to the cardiomy reservoir ^{38,39}. Neurocognitive dysfunction after cardiac surgery is associated with retransfusion of cardiomy suction blood and is one of the main reasons for decreased quality of life post-operatively ^{40,41}. Micro-

particles can cause micro-embolisms in other organs, such as the kidneys and impair their function ^{36,42}. Cardiotomy suction is additionally associated as one of the main sources of haemolysis ^{35,43,44}. A complete avoidance of cardiotomy suction would probably decrease not only micro-emboli, but also the inflammatory reaction and haemolysis ^{29,34,35}.

In summary, cardiotomy suction blood is far from clean and contains a substantial fraction of potential embolic substances, haemolytic blood, activated platelets and pro-inflammatory substances that can impair haemostasis and increase the inflammatory response. This should at least lead to re-evaluating the routine use of cardiotomy suction during low risk cardiac surgical operations in which there is no anticipated large amount of intra-operative blood loss, such as primary aortic valve replacement or coronary artery bypass grafting (CABG). In an effort to ameliorate some of these potentially detrimental effects of cardiotomy suction blood, strategies were developed for specific lipid, red blood cell and leukocyte filtration while still being able to recuperate red blood cells. The anticipation was that application of these alternative strategies would reduce or ideally remove the pro-embolic, pro-inflammatory, pro-fibrinolytic and pro-coagulatory elements of the cardiotomy suction blood.

Role of leukocyte depletion filters in improving the cardiotomy blood quality

One approach to improve the quality of cardiotomy suction blood is to eliminate or reduce micro-embolization. This can be achieved by the application of fat or leukocyte depletion filters. Fat filters can actually decrease the incidence of embolization, but they do not have an effect on the pro-inflammatory reaction ^{39,45-47}. Leukocyte depletion filters in turn might improve the blood quality by the removal of activated leukocytes but also fat and other particles from the collected blood. Activated leukocytes play a major role in the initiation of a systemic inflammatory response and organ reperfusion injury in patients undergoing cardiac operations with cardiopulmonary bypass ⁴⁸⁻⁵⁰. In recent decades, the concept of leukocyte depletion has been introduced to cardiac surgery to remove leukocytes by means of various strategies. These include arterial line filtration, removal from the local blood cardioplegia circuit, during the reperfusion phase on CPB, from banked blood or from the salvaged blood and residual heart-lung

machine blood⁵¹. Furthermore filtration of retransfused blood salvaged by a cell saver device has also been applied⁵²⁻⁵⁵. In theory, if blood from the cardiomy suction reservoir is retransfused to the patient through a leukocyte depletion filter, the release of pro-inflammatory agents is reduced and the plasma fraction of the blood is retained (instead of lost when for example a cell saver is used)⁵⁶. However, although leukocyte depletion is often reported as a successful method in reducing inflammation, nearly all of the clinical trials have failed to demonstrate clinical benefits on overall patient outcomes such as morbidity, mortality, and hospital stay^{50-52,57-59}. Possible reasons why existing studies did not find a positive effect of the filters are the small number of patients in the existing studies, poor quality of the trials (non-randomized), different patient populations and focus on laboratory effects instead of clinical endpoints. Furthermore the studies varied in the application of leukocyte filtration regarding the timing (during cross-clamp and/or during reperfusion), duration of filtration (intermittent versus continuous), regarding the position of the filters (arterial and/or cardioplegic line), frequency of filter change due to filter capacity exhaustion and to a lesser extent the type of filter used^{51,59}. But there is some evidence that points to specific patient subgroups that could benefit from leukocyte depletion. These are patients with chronic obstructive pulmonary disease, high-risk patient groups (left ventricular hypertrophy, reduced left ventricular ejection fraction, cardiogenic shock) and high-risk procedures (coronary bypass and valve surgery with cross clamp times greater than 120 minutes, paediatric cardiac surgery, emergency coronary artery bypass or cardiac transplantations)^{58,60}. But, again, recent studies with leukocyte depletions in these specific patient groups and a Cochrane review did not show a significant improvement in clinical outcomes^{49,61-63}. The method of leukocyte filters on the CPB circuit is not recommended in the current guidelines¹.

Role of cell savers in improving cardiomy blood quality and as blood sparing strategy

Cell savers are used in cardiac surgery to recover intra-operative shed blood in order to reduce the need for allogeneic blood transfusions. The cell saver was introduced by the end of the 70's in the past century in the United States as a means to bypass the cardiomy suction in cardiac surgery. One of the first randomized controlled trial with an intra-operative cell saver was performed in 1993 in the United States⁶⁴. This

small study showed that intra-operative use of a cell saver as alternative of cardiomy suction decreased the exposure to allogeneic blood transfusions in comparison to discarding the peri-operative shed blood. At the end of the 20th century the use was expanded to Europe when the Health Services Circular “Better Blood Transfusion” in Great Britain advocated its use ^{65,66}.

The process of intra-operative cell salvage can be divided into three phases: blood collection, blood washing, and re-transfusion. Blood from the operative field is collected, together with other contents of the pericardial cavity, by the use of a double-lumen suction tube. One lumen suctions blood from the operative field and the other lumen adds a volume of heparinized saline to the salvaged blood. The blood is then passed through a filter and collected in a reservoir for processing (hence the need for anticoagulation). The blood is centrifuged and then washed with a solution. The process removes plasma, platelets, leukocytes, free hemoglobin and heparin ⁶⁷. This results in a concentrated amount (haematocrit between 50-80%) of recovered red blood cells ready to be retransfused to the patient. Contrary to the use of cardiomy suction alone, collection of shed blood is thus possible outside the time frame of the CPB period with the use of a cell saver e.g. even before application of full dose heparin and after application of protamine. Intra-operatively used, cell saver can also process the remaining volume in the CPB circuit. Furthermore, the cell saver can be employed during the post-operative period to process shed mediastinal blood. With this approach the possibility to recover shed blood is extended.

The Society of Thoracic Surgeons and the society of Cardiovascular Anaesthesiologists have recently updated their blood conservation clinical practice guidelines. Accordingly the use of cell savers is a class I recommendation in all patients except in those with infections or malignancy ¹.

The influence of processing cardiomy suction blood with a cell saving device on the quality of the blood has been investigated in several studies. Quality aspects of collected and/or retransfused blood studied vary between free haemoglobin ⁴⁴, heparin ⁶⁸, platelet, leukocyte ⁶⁹⁻⁷¹ and fat elimination ^{39,42,47,72,73}. Other parameters that have been extensively investigated are the effect of cell salvage on pro-inflammatory cytokines ^{37,74-77} and haemostasis ^{67,69,76-79} in the collected and patients blood. Cell salvage can result in the activation of white blood cells leading to the release of

inflammatory mediators. However, the centrifugation and the washing process reduces the concentration of these white blood cells and inflammatory mediators⁷⁵. Transfusing blood from the cardiotomy reservoir after centrifugation leads to a decrease in systemic vascular resistance and can lead to a decreased afterload which can improve post-operative cardiac function³⁷.

Recently focus has shifted to the function of red blood cells processed by the cell saver in cardiac surgery. This quality aspect of blood was initially investigated in stored red blood cells. The changes that were found in these stored red blood cells were called “storage lesions”⁸⁰. RBC function examined is the cell membrane deformability or the ability for the cell to elongate when exposed to shear stress while being forced through a thin channel^{81,82}. RBC cell membrane elasticity and the ability to change shape are important qualities of the RBC’s to pass through small capillaries. Impaired RBC membrane deformability is associated with reduced flow in the microcirculation, as well as reduced regional blood flow and reduced oxygen delivery⁸³. RBC aggregation is an important, shear dependent, determinant of blood viscosity. RBC aggregation and deformability are affected by blood storage⁸⁴. Moreover, RBC function can be studied by looking at the depletion of the 2,3-diphosphoglycerate (DPG) and adenosine triphosphate (ATP) content. 2,3-DPG is necessary for regulating oxygen delivery and ATP is the energy source for the overall functioning of the red blood cell. In the limited studies on red blood cell function in cardiac surgical patients, the cell salvage process does not seem to impair the overall red blood cell function, although there appears to be a reduction in the deformability of the red blood cells. There are contradictory results on the effect of cell salvage on the 2,3-DPG content^{52,79,85}.

Two recent meta-analyses demonstrated a risk reduction for blood transfusion during cardiac surgery using intra-operative cell salvage^{86,87}. However there was great heterogeneity between the reviewed studies. This was mainly because of the different initial objective of cell saver deployment. In studies where cell savers were predominantly used for blood conservation, a comparison was made between discarding blood before and after the CPB time period and between collecting, washing and re-transfusing this otherwise discarded blood^{88,89}. However, in a number of other studies, cell savers were mainly used for organ protection and a reduction of the inflammatory response that is associated with cardiopulmonary bypass^{41,53,90}.

In these studies the comparison was typically made between washed and unwashed blood both of which were returned to the patient (for example cardiotomy suction blood). These different strategies likely affect the possible reduction in transfusion requirements. Studies on organ protection and cell savers were performed to try to eliminate embolic load of the cardiotomy suction blood ^{41,53}. Intra-operative use of cell savers can decrease the fat-related micro-embolic load significantly ^{39,42,45,91}. The processing of blood by a cell saver reduces fat micro-embolism to the central nervous system and can thus decrease the incidence of neurological complications after cardiac surgery procedures ^{41,42}. However, some published studies doubt the theoretical benefit when it comes to less complications ⁵³.

Another reason for the heterogeneity between the reviewed studies, mainly regarding the blood transfusion data, is the different time frame period of cell saver employment in nearly all studies (table 1).

Table 1: Time frame of cell saver use in recent studies

Study	Pre- or post-CPB	CPB	Residual CPB blood	Post op
Attaran ⁹²	+	-U [§]	-	-
McGill ⁸⁸	+	-	+	-
Reyes ⁹³	+	-	+	-
Klein ⁸⁹	+	-	+	+
Murphy ⁹⁴	+	-	-	+
Damgaard ⁷⁵	+	+	+	-
Diprose ⁹⁵	+	+	+	-
Laub ⁶⁴	+	+	+	-
Weltert ⁹⁶	+u	+¶	+¶	+
Jewel ⁹¹	u	+	+	-
Vonk ⁹⁷	-	+	+	-
Svenmarker ⁹⁸	-	+	-	-
Djaiani ⁴¹	-	+	-	-
Westerberg ⁹⁹	-	+	-	+
Rubens ⁵³	-	+	-	+
Dalrymple ¹⁰⁰	-	-	+	+
Sirvinskas ¹⁰¹	-	-	-	+

Pre- or post-CPB, use before or after cardiopulmonary bypass; CPB, use during cardiopulmonary bypass; Post-op, use during intensive care stay.

-= not used; += used; u = unclear if used; ¶= includes 35% off pump cardiac surgery; §, includes 20% off pump

This variation in cell saver deployment, as shown in table 1, is of course partly understandable a result of the difference in initial purpose of cell saver deployment: blood conservation^{64,88,89,94,96,97} or organ protection^{41,53}. Others have used the cell saver in order to investigate whether there is a reduction of inflammatory markers or formation of haemolytic blood^{98,99}. When used in such a manner, the cell saver is typically only used during the CPB period, with some studies also processing the remaining CPB volume.

When a cell saver is mainly used as a blood transfusing sparing strategy the time period is usually the entire operation, and sometimes beyond^{96,97}. Processing the cardiotomy suction blood with a cell saver during CPB only has no significant effect on blood conservation but can increase the need for fresh frozen plasma transfusion^{41,86}. Some studies were a reflection of the current operating procedures in that specific institution^{89,94}. Only a few authors use the cell saver to collect all shed blood during the operation, not only blood lost during CBP time^{96,97}. Deployment of a cell saver can only be optimal as a blood conservation strategy when all shed blood is processed, is the stated argument. Cell savers have therefore also been used, as an extension of this argument, to process and re-transfuse post-operative shed mediastinal blood in addition to intra-operative use alone^{53,89,94}. One study centered on this topic⁹⁶.

Furthermore, the amount of blood processed and thus the amount of RBC retransfused to the patient, by the cell savers varies substantially in the above mentioned studies making firm conclusions on the effect of the use of the cell saver on transfusion requirements difficult. Another methodological problem in cell saver studies is the lack of data on collected blood volume and final processed blood volume. These volumes, however, are important to calculate the crude extraction ratio and thus understand the full efficacy of the cell saver.

Despite the increasing pro arguments for the use of cell savers during cardiac surgery there are still studies that conclude that a cell saver should not routinely be used in low risk cardiac surgery and that it's use should perhaps only be implemented in medium to high-risk surgery. Use in low risk surgery is not blood sparing and not cost effective^{92,93}. Alas, these studies lack methodological rigor and include a large proportion of off-pump cardiac surgery or the cell saver is not used during CPB (table 1). Two recent studies specifically show that the cell saver can also be effective in low to intermediate risk cardiac surgery^{96,97}.

Investigational questions

In the light of the questions raised in the discussion above we wanted to investigate whether the quality of the collected and retransfused blood in cardiac surgery could be improved. Furthermore, the question remained whether cell savers, or the use of filters, can reduce allogeneic blood transfusions in cardiac surgery. In this thesis we have tried to lift the veil on some of these matters.

Outline of the thesis

The first part of this thesis serves as an introduction into the different possibilities and difficulties in blood sparing strategies in cardiac surgery. The main focus on improving cardiotomy suction blood by filtration and use of a cell saver device is introduced. In **chapter 2** the effect of cell saving, leukocyte depletion filters and/or their combination on transfusion requirements in cardiac surgery is described. In **chapter 3** the question whether the quality of processed blood is affected when larger quantities of blood are processed in multiple intra-operative processing runs of a cell saver device is described. In **chapter 4** whether additional post-operative collection and processing of mediastinal shed blood with a cell salvage device reduces the number of allogeneic blood transfusions compared to intra-operative cell salvage alone is described. In **chapter 5** the leukocyte and fat removal properties and the biocompatibility of three different filters is described. Finally in **chapter 6** whether the use of a cell saver influence red blood cell function and if retransfused processed blood affects RBC function in patients is described. **Chapter 7** provides a summary, general conclusion and discussion on future perspectives.

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