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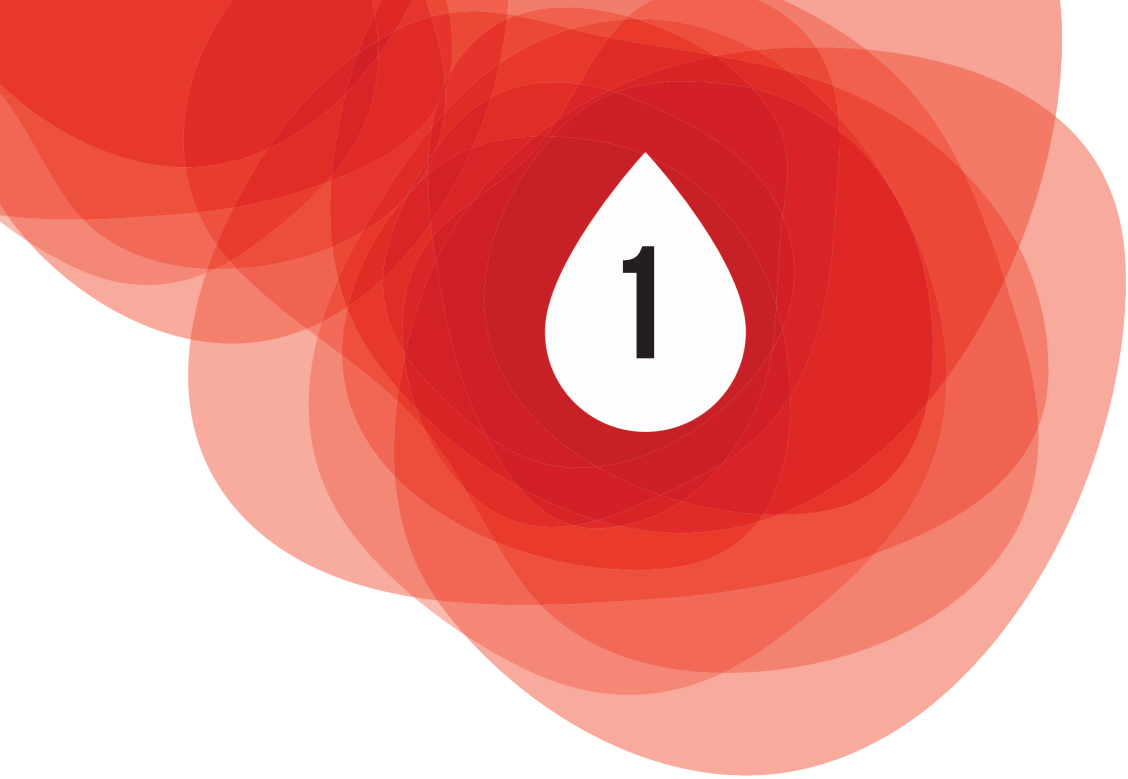
Publication date
2022



GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

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The efficacy of red blood cell transfusion in the critically ill

Red blood cells

Red blood cells (RBCs) are the most common cells of the body. They are shaped as a biconcave disk with a diameter of approximately 6.2 – 7.5 micrometers.[1] Their main function is to deliver oxygen to the tissues. Therefore these cells contain hemoglobin, which binds oxygen in the lungs and releases the oxygen in the peripheral tissues.[2] RBCs are extremely elastic to be able to move through very narrow capillaries.[2] The production of RBCs takes place in the bone marrow.[2] Approximately 2-3 million new RBCs are produced every second. To have maximum space for hemoglobin (Hb), RBCs lose their nucleus and organelles during maturation.[2] In a healthy individual RBCs circulate for about 100-120 days, after which they are cleared from the circulation by the spleen or the liver.[2] In this way 0.8% of the circulating RBCs are replaced every day.

Anemia in the critically ill

In healthy individuals, the production and clearance of RBCs is balanced. However, in critically ill patients, this balance is often disturbed, leading to anemia.[3] Therefore, anemia is a very common problem at the intensive care unit (ICU). At admission, 60% of the patients have a Hb level below 9.0 g/dL (reference range M; 13.0-18.0, F; 11.5-16.5) and this percentage increases during ICU stay.[4] Anemia at the ICU is often multifactorial and can be caused by a decreased production of RBCs, blood loss or increased clearance of RBCs or a combination of those. However, it is thought that the most important cause of anemia in the critically ill is anemia of inflammation (AI).[3,5] AI is characterized by a decreased production of RBCs due to a reduced iron availability and impaired erythropoietin (EPO) synthesis and sensitivity.[6–8] At the other hand, inflammation leads to enhanced clearance and a shorter lifespan of RBCs.[3,8] AI in the critically ill patient is different from AI in patients with chronic inflammatory diseases and is known for its accelerated course. At the ICU, AI develops within days, which is too rapid to be accounted for by deficient erythropoiesis which is mostly seen in chronic diseases, therefore clearance of RBCs seems to be the major cause.[8] However, due to a deficient erythropoiesis in AI, it is impossible to compensate for the increased clearance.

RBC transfusion at the ICU

Anemia in critically ill patients is associated with adverse outcomes, such as failure of liberation from mechanical ventilation, type 2 myocardial ischemia, and increased mortality.[9,10] Therefore, current practice is to treat anemic patients with RBC transfusions. At the ICU, more than 25% of patients receive at least one RBC transfusion.[4] The aim of a transfusion is to improve tissue oxygenation by increasing the number of circulating RBCs. The efficacy of a RBC transfusion is defined by the number of donor RBCs still circulating 24 hours after transfusion, which is called the 24 hours- post transfusion recovery (PTR). However, despite its relevance, the PTR of RBC transfusions has not been well studied. Since inflammation plays an important role in the clearance of endogenous RBCs, leading to anemia, inflammation potentially also reduces the

PTR of a RBC transfusion in the critically ill.

Adverse events of RBC transfusions in the critically ill

RBC transfusions are associated with adverse events, which particularly holds true for the critically ill compared to other patient categories.[11,12] The mechanisms behind these adverse events are largely unknown, but may be related to the inflammatory state of the critically ill patient. The presence of an inflammatory state in the recipient has been shown to be a risk factor for the development of transfusion related acute lung injury (TRALI).[13] Also in patients that do not meet all the criteria for TRALI, an extra 'hit' by the RBC transfusion can exacerbate pulmonary inflammation and pulmonary vascular leakage, potentially resulting in transfusion related lung injury.[14,15] During inflammation, immune cells, endothelial cells and the coagulation system are activated[16,17], an extra hit by the RBC transfusion potentially leads to further activation, which could play a role in the development of transfusion related adverse events. Later in this introduction this will be discussed in more detail.

This thesis will address 2 important aspects of RBC transfusion which determine the efficacy of a RBC transfusion in the critically ill recipient. First, the PTR of donor RBCs in the critical ill recipient will be discussed. Second, several possible mechanisms for adverse events are investigated.

Part I. PTR of RBC transfusion in the critically ill.

Clearance of endogenous RBCs

Since RBCs lack a nucleus and mitochondria, they are not able to undergo apoptosis.[2] Therefore, RBCs need to have another clearance mechanism at the end of their lifetime. Studying RBC clearance signals *in vivo* is difficult. RBCs that express clearance signals are thought to be rapidly cleared and will therefore circulate very shortly. This makes it difficult to isolate and study cells that are prone for clearance. The mechanisms by which senescence RBCs are recognized are therefore still not fully unraveled and mostly based on *in vitro* and animal studies.

Under normal conditions the clearance of RBCs mostly takes place in the spleen. The spleen has the ability to filter the blood and remove old or damaged RBCs.[18–20] Circulating RBCs pass through the spleen numerous times during their lifetime. In the red pulp of the spleen, RBCs have to pass through very narrow inter-endothelial slits to enter the venous circulation. To do so, RBCs have to be very flexible. However, during aging, RBCs become more rigid and when the RBCs are no longer able to pass through the inter-endothelial slits they will get captured in the spleen and will be phagocytosed by red pulp macrophages.[18–20] The decrease in deformability is most likely triggered by cytosolic Ca^{2+} influx induced by cell stress (oxidative stress, shear stress, osmotic stress).[21–23] The increased intracellular Ca^{2+} level will lead to the efflux of K^+ and water.[24] The efflux of water results in cell shrinkage and decreased deformability of the RBCs.[24] Increased Ca^{2+} levels also induce membrane vesiculation resulting in smaller and denser cells

which will further decrease RBC deformability.[25]
Also, it is thought that the presence of so called "eat-me" signals on the cell membrane of RBCs can trigger phagocytosis by red pulp macrophages.[20] One of those "eat-me" signals is presumed to be phosphatidylserine (PS). The cell membrane of RBCs normally consists of a bilayer with an asymmetrical distribution of phospholipids, with PS mainly exposed on the inner leaflet.[26] In RBCs reaching the end of their lifespan, the increased intracellular Ca^{2+} levels induce PS externalization.[21,27] PS has been recognized as an "eat-me" signal, since macrophages can bind to PS, direct or indirect.[28–31] Other potential "eat-me" markers are CD47, which is a marker of "self" on the RBC membrane, and band-3 clustering. CD47 is found in two different conformations. In the resting conformation, CD47 binds SIRP-alpha present on macrophages and thereby inhibits phagocytosis. Therefore, in this conformation CD47 is a "don't eat me" signal. However, the conformational change of CD47 induced by oxidative stress changes the molecule from a "don't eat me" to an "eat me" signal. As an "eat me" signal, thrombospondin-1 can bind CD47 and changes the interaction with SIRP-alpha leading to phagocytosis.[20,32] Band-3 is a transmembrane protein that under the influence of oxidative stress forms clusters. This is thought to result in the binding of natural occurring antibodies (Nabs) and subsequent complement activation leads to the recognition and clearance of the RBC by macrophages.[33]

Clearance of endogenous RBCs in inflammatory conditions

During their lifetime, RBCs continuously undergo mechanical and oxidative stress resulting in RBC senescence.[34] Inflammation accelerates this process and shortens RBC lifespan, probably induced by circulating cytokines and increased oxidative stress.[3] Inflammation and sepsis result in an increase of RBC intracellular calcium levels, decreased deformability and increased expression of eat-me signals.[22,35–37] Furthermore, some research also points towards endothelial adhesion and trapping of RBCs in organs during inflammation. This phenomenon is mostly known from other medical conditions such as sickle cell disease[38], malaria[39] and diabetes mellitus[40], but has also been described in response to inflammatory stimuli.[41–43]

Post transfusion recovery

After transfusion, donor RBCs are probably susceptible for clearance by the same mechanisms as endogenous RBCs. Clearance of donor RBCs post transfusion would reduce the yield of a transfusion by reducing the increase of circulating RBCs in the recipient.

To study the PTR of a RBC transfusion product, it is necessary to distinguish the donor RBCS from the endogenous RBCs in the circulation after transfusion. For that purpose, several methods have been developed. The gold standard is labelling a part of the RBCs in the transfusion product with Chromium-51,[44] however this radioactive label is nowadays forbidden in the Netherlands. It is also possible to distinguish the blood from the donor from that of the recipient based on minor differences between blood type.[45] The advantage of this method is that it does not require any RBC labelling. However, a mismatch is not always present and multiple transfusions interfere in the differentiation. Biotin (vitamin B6) labelling is a new method to study PTR without using

radioactivity. Before transfusion, a part of the RBCs are labelled with biotin. In a blood sample, these RBCs can be stained with streptavidin and analysed using flow cytometry.[46] The PTR is one of the quality criteria of a RBC transfusion product and has to be at least 75%.[47]

Post transfusion recovery during anemia of inflammation

To determine the quality of a RBC transfusion product, the PTR has to be studied in healthy volunteers with autologous blood.[48,49] However, this situation is not comparable with the clinical situation in which the recipient is anemic due to a certain illness and receives an allogenic RBC transfusion. Thereby, only a limited number of studies investigated the PTR during illness and no studies are done in the critically ill. The PTR has been studied in volunteers after lipopolysaccharide (LPS) injection to mimic critical illness.[50] However, the impact of LPS on RBC production and clearance has a limited comparability to AI. Furthermore, some small clinical studies have been done in hematology patients. These studies show a 24 hour PTR of 60% to 100%,[45,51] suggesting that clearance is increased during illness. However, the etiology of anemia in hematology patients is different from patients with AI. Also, the clinical condition is different. As inflammation reduces the lifespan of endogenous RBCs in the critically ill it can be hypothesized that inflammation also hampers survival of donor RBCs, resulting in a reduced PTR. Donor RBC clearance is thought to take place in the spleen, but this has never been well studied. Besides clearance in the spleen, trapping of donor RBCs in other organs can also lower the PTR. It has previously been shown that endotoxemia results in increased trapping of donor RBCs in the lung and the kidney in a rat model. *In vitro* and animal studies showed adherence of stored donor RBCs to the vascular wall.[52–54]

Factors influencing post transfusion recovery

Improving the PTR would increase the efficacy of a transfusion. Besides the condition of the recipient, also donor characteristics and the transfusion production process can have impact on the PTR.

The donor. Although an obvious explanation is still lacking, it is well-accepted that donor to donor variation plays a role in transfusion product quality.[55,56] Genetic RBC polymorphisms seem to play a role,[57,58] but also donor sex and age have an impact on RBC product quality.[55,59] In an animal model, blood from male donors showed higher in bag hemolysis with a concomitant lower PTR compared to female donors.[60] Differences in hormonal status are a potential explanation for the differences that are observed between male and female donors.[60,61] Human aging also leads to RBC changes, such as a decrease in the activity of the enzyme glucose-6-phophate dehydrogenase (G6PD), resulting in an increased vulnerability for oxidative stress.[62–65] Increased donor age results in more hemolysis in the transfusion unit during storage.[59,60] So far, no studies on the impact of donor age on PTR have been performed.

The production process and storage of RBC units. In the production process, the RBCs from the donor are first separated from the other blood components and then stored in an additive

solution at 4°C. In the Netherlands, Saline Adenine Glucose Mannitol (SAGM) is used as additive solution. The RBC units can be stored up to 35 days.[66] However, during storage, changes occur to the RBCs, these changes are called "storage-lesions".[67] Over time, the glucose is consumed and 2,3-DPG and ATP levels are decreased.[67] RBCs also produce extracellular vesicles (EV) during storage, these are small membrane enclosed vesicles which accumulate in the transfusion unit.[68] Furthermore, a small part of the RBCs break down (hemolysis) leading to increased potassium levels and free Hb.[67,69] A large randomized controlled trial did not find a difference in mortality between critically ill patients receiving a RBC transfusion after a short or standard storage duration.[70] However, this does not mean there is no difference in efficacy between RBC units that have been stored for different duration. The impact of storage duration on PTR has been assessed in two volunteer studies and one patient study. These studies all showed a slight decrease in PTR with increased storage duration. However, the PTR stayed above the critical limit of 75%.[48,50,51]
An intervention which could potentially reduce the impact of storage lesions is washing of the stored RBCs. Washing removes the compounds that accumulate during storage.[71] The impact of washing on the PTR has been studied in healthy swine, which did not improve the PTR. [72] Also, new (rejuvenating) additive solutions are studied to reduce the storage lesions.[73] Recently, the FDA approved additive solution-7 (AS-7) after research showed an improved PTR compared with currently used solutions.[74]

The impact of donor RBC quality on the PTR in the critically ill. More research is needed on the impact of donor RBC quality on the PTR in the critically ill patient. The inflammatory environment in the critically ill patient with high levels of cytokines and oxidative stress probably places an extra burden on the donor RBCs after transfusion. This could render donor RBC quality before transfusion in the critically ill recipient even more important than in other patient categories. The impact of interventions improving donor RBC quality on outcome is potentially greater in the critically ill. Therefore it is important to study the impact of these factors on PTR during critical illness.

Until now, I discussed factors influencing the PTR. However, also the occurrence of adverse events will influence the efficacy of a RBC transfusion. The aim is for a RBC transfusion product with a maximum PTR and minimal adverse events. Mechanisms of transfusion associated adverse outcome are largely unknown, it can be hypothesized that an impaired PTR as a result of increased trapping or hemolysis, may contribute to adverse effects associated with transfusion. In addition, adverse effects may be unrelated to PTR but may result from other mechanisms.

Part II. Adverse events of RBC transfusion in the critically ill

Adverse effects of transfusion

Due to several safety measures, adverse events of RBC transfusion became rare, in 2018

0.44% of RBC transfusions resulted in an adverse event in the Netherlands, with a severe reaction in 0.02%.[75] Nevertheless, adverse effects of RBC transfusions are still reported and as mentioned before more often in the critically ill.[12] Adverse events include hemolytic transfusion reactions, transfusion related lung injury (TRALI),[13,76] transfusion associated circulatory overload (TACO)[77], transfusion- related immunomodulation (TRIM)[78] and organ failure[12]. Furthermore, also associations are reported between RBC transfusions and certain clinical conditions, such as thrombosis and susceptibility for bacterial infections. [79–83] The precise pathophysiological mechanism behind these adverse events is unknown. However, especially in TRALI, a "two-hit" hypothesis has been assumed. In which the first hit is the inflammatory condition of the recipient and the second hit the transfusion.[13] This would also explain the higher incidence of TRALI in critically ill patients.[13] Inflammation can also be the key in the pathophysiology of other adverse events. During inflammation the immune system, coagulation system and endothelium are activated, an extra 'hit' by the RBC transfusion may exacerbate inflammation, potentially resulting in transfusion related adverse events.[52,80,84] Therefore, the recipients clinical condition can be a risk factor for transfusion related adverse events.

Link between donor RBC clearance and adverse events

Besides clearance in the spleen, RBCs can also be cleared from the circulation due to hemolysis. RBCs can hemolyze in the bag during storage as well as after transfusion.[85,86] Both will result in the release of the RBC intracellular contents into the blood plasma, releasing free Hb and heme into the circulation, which are potential sources of oxidative stress.[86,87] Especially when they cannot be neutralized by their scavenger proteins, haptoglobin and hemopexin.[85] Free Hb is also a scavenger for nitric oxide (NO).[88,89] An increase in free Hb will therefore lower the bioavailability of NO, leading to increased vasoconstriction, decreased organ perfusion and potentially organ injury.[88,89] Furthermore, hemolysis results in the release of iron into the circulation.[85] After transfusion we see a transient increase in iron in the circulation of critically ill patients.[90] This iron load can be harmful for patients with a bacterial infection, since iron can increase bacterial growth.[91–93]

As mentioned earlier, *in vitro* and animal studies show that donor RBCs can also get trapped in the microvasculature and that trapping of RBCs is probably increased during inflammation.[41–43,52–54] Donor RBCs can get trapped in the microcirculation due to reduced donor RBC deformability[94,95] or due to adherence to the vascular wall.[96] Trapping of RBCs in the organs can potentially impair the microcirculatory flow or reduce tissue oxygenation and thereby induce organ injury.[97]

Relation between extracellular vesicles and transfusion associated adverse outcome

RBC-derived extracellular vesicles (EVs) are small membrane-enclosed vesicles with a diameter of less than 1.5 μm.[98] The formation of RBC-derived EVs occurs when the asymmetry of the cell membrane is lost, and is triggered by different stimuli, including oxidative stress and shear stress.[98,99] RBC-derived EVs are released from endogenous circulating RBCs, as well as during storage, the latter resulting in the accumulation of EVs in transfusion units.[68] EVs derived from

donor RBCs have been related to activation of coagulation,[100–102] endothelial activation[103] and immunomodulation,[104,105] and therefore may play a role in the observed adverse effects that occur after blood transfusion. In a model of human endotoxemia, it is shown that after transfusion of a stored RBC unit containing a high amount of RBC-derived EVs, the concentration of circulating RBC-derived EVs increases.[68] Furthermore, in mice it has been shown that the injection of RBC-derived EVs induced the production of proinflammatory cytokines during endotoxemia, which did not occur in healthy mice.[106] Thereby, RBC-derived EVs might explains the higher incidence of adverse events of blood transfusions in the critically ill.

Potential effector cells in the patient

Endothelium and glycocalyx. Endothelial cells line the inner wall of the vessels. The apical surface of these cells are covered with the glycocalyx, a thin layer of proteoglycans, glycoproteins and glycolipids with a barrier function. It protects the endothelial cells from oxidative stress and provides anti-coagulant and anti-adhesive effects. Cytokines and reactive oxygen species (ROS) released during inflammation can cleave parts of the glycocalyx.[16] Inflammation can also directly activate the endothelial cells .[16] Therefore, critically ill patient often have an activated endothelium.[107] Since the vascular endothelium and glycocalyx are among the first that interact with the donor RBCs after transfusion, these structures might play a role in the pathophysiology of adverse events. RBC transfusion is associated with increased biomarker levels of endothelial cell activation in hematological (syndecan-1) and pediatric patients (soluble intracellular adhesion molecule- 1, macrophage inhibitory factor).[108,109] Endothelial cell activation can lead to increased endothelial permeability with neutrophil extravasation and capillary leakage, potentially resulting in organ injury.[14] Furthermore, the activated endothelium enables the adhesion of RBCs which can result in trapping of RBCs.[41–43]

Platelet function and the coagulation cascade. RBC transfusions are linked to thrombo-embolic events.[83,110,111] Thrombo-embolic events occur after activation of the coagulation system, resulting in (micro)thrombus formation.[112] This would suggest that RBC transfusion contributes to the activation of the coagulation cascade. An *in vitro* study showed that platelet activation and aggregation are increased after transfusion[79] and supernatant of stored RBC units can induce thrombin generation.[113] Platelet activation can be the result of a direct interaction with RBCs, for example due to PS exposure on the RBC membrane. PS externalization results in a procoagulant cell surface which support thrombin generation.[114] Also other components in the transfusion unit can contribute to the activation of the coagulation cascade, such as free Hb and EVs. Free Hb can lower the bioavailability of NO, which prevents NO-mediated suppression of activated platelets.[115] RBC-derived EVs are also related to hypercoagulability. Hereby, the exposure of PS on EVs probably plays a procoagulant role.[100–102,113]

Immune system. RBC transfusion can influence the immune response, which is called TRIM, and can result in a pro-inflammatory response as well as in a immunosuppressive response.[78] The pro-inflammatory response is linked to the occurrence of organ injury whereas the

immunosuppressive response is linked to nosocomial infections.[82,91,116–118] The factors that mediate TRIM are unknown. Proposed mediators include EVs, free heme, iron, bioactive lipids and residual white blood cells.[78] Experimental data suggest that RBC transfusion can result in the activation of neutrophils,[119,120] inflammatory cytokine release[121] and monocyte activation[104]. But also an immunosuppressive response has been found with decreased natural killer cell activity and anti-inflammatory cytokine release.[78,122]

Effect of RBC transfusion on oxygen delivery

The aim of a transfusion is to increase oxygen delivery and prevent hypoxia. Therefore it is important that a RBC transfusion does not only increase the number of circulating RBCs but also increases the actual oxygen delivery to the tissues. However, the effect of a RBC transfusion on the tissue oxygenation of critically ill patients is unclear.[123] The oxygen delivery to the tissues does not only depend on Hb level and oxygen saturation, but also on tissue perfusion and microcirculatory flow.[124] The adverse events described above, such as trapping of donor RBCs and the effects on the endothelium or coagulation, potentially contribute to a transfusion related deterioration of the microcirculation instead of an improvement. Strategies to prevent the occurrence of transfusion related adverse events can therefore potentially also result in better tissue oxygenation and therefore efficacy of RBC transfusion.

Aim of this thesis

All together, we hypothesize the disease severity of the critically ill recipient can have an important impact on the efficacy of RBC transfusions. It can interfere with the yield of a RBC transfusion and reduce the PTR, but potentially also plays a crucial role in the development of adverse events after transfusion. Knowledge about the impact of inflammation and disease severity on the efficacy of RBC transfusion is important to be able to weight the potential benefits against the harms and make a well-considered transfusion decision for the critically ill patient and is also important to improve RBC unit quality.

The aim of this thesis is to extent the knowledge about 1) in vivo RBC survival and interventions to improve the PTR in the critically ill 2) red blood cell transfusion related adverse events in the critically ill.

Outline of the thesis

Part 1. PTR of a RBC transfusion in the critically ill

In chapter 2 we investigated the survival of donor red blood cells in an animal model and in critically ill patients. We studied the impact of disease severity on the PTR, furthermore we tried to clarify the clearance pathways and the role of calcium.

In chapter 3 we studied the effect of sepsis in the recipient on donor red blood cell survival and investigated a potential intervention to improve transfusion outcome (washing) in a rat

pneumonia model.

Part 2. Adverse events of RBC transfusion in the critically ill

In chapter 4 we investigated possible clearance pathways of extracellular vesicles released during storage of red blood cells in an endotoxemia model in volunteers.

In chapter 5 we studied the effects of a RBC transfusion on biomarker levels of endothelial cell activation, inflammation and coagulation in critically ill patients and the role of disease severity.

In chapter 6 we studied the effects of red blood cell transfusion on platelet function in the critically ill.

In chapter 7 we looked at the effects of transfusion on the microcirculation and the correlation with disease severity.

The results of this thesis are summarized in chapter 8 and in chapter 9 we discuss the results.

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