Clinical aspects of blood activation in open-heart surgery
van den Goor, J.M.M.H.

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Chapter 1

General introduction, aim and outline of the thesis
Open-heart surgery in the Netherlands

In the Netherlands, open-heart surgery is performed in sixteen hospitals. For instance, 15,794 open-heart operations were carried out in 2006, including paediatric cardiac surgery, bypass surgery with and without cardiopulmonary bypass (CPB), and valve surgery.\textsuperscript{1}

Blood activation during cardiopulmonary bypass

In a historical perspective, the first open heart surgery procedures were performed without the aid of a heart-lung machine.\textsuperscript{2} After the development of a heart-lung machine\textsuperscript{3} and the introduction of heparin as an anticoagulant,\textsuperscript{4} open-heart surgery procedures assisted by cardiopulmonary bypass became possible. In addition, by these developments also more complex cardiac surgical procedures could be performed.\textsuperscript{5} One of the major disadvantages of the first generation of the heart-lung machine was considerable activation of patient blood. This activation resulted in hemolysis, activation of blood cells, contact activation, complement activation, coagulation activation, excessive use of blood products during and after CPB, postoperative inflammation etc., resulting in a high mortality.\textsuperscript{6,7}

Compared to the first generation of heart-lung machines, the biocompatibility of the current generation of heart-lung machines has improved considerably. For instance, by down-scaling the total size of the extracorporeal circuit, the body foreign surface area contacting the patient blood became reduced. As a consequence, the priming volume of the extracorporeal system was reduced, resulting in nowadays usage of artificial prime fluids requiring no donor blood or blood products. Other improvements included the introduction of arterial and cardiotomy filters, and improving the biocompatibility of the surface of the extracorporeal circuit.\textsuperscript{8-11} Despite the before mentioned improvements, however, the heart-lung machine is still considered to be detrimental to patients. Therefore, alternative procedures have been developed avoiding the use of a heart-lung machine during open heart surgery ("off pump surgery"). There is still no consensus, however, with regard to the question whether or not "off pump surgery" is an overall improvement to patients compared to "on pump surgery".\textsuperscript{12-20}
General introduction, aim and outline of the thesis

In all patients undergoing open-heart surgery, “on pump” (assisted by CPB) as well as “off pump surgery” (without CPB), wound blood collects in the pericardial cavity and is removed by suction. Wound blood, also called pericardial, cardiotomy or shed blood, is characterized by excessive blood activation when compared to systemic blood activation.\(^{21-24}\) In general, this autologous wound blood is retransfused into the systemic circulation to reduce the use of heterologous blood or components thereof. It is still unclear to which extent retransfusion of wound blood into the systemic blood contributes to systemic blood activation and brain damage during and after bypass.\(^{23,25}\)

**Current controversial topics in cardiopulmonary bypass**

At present, further reduction of the priming volume by using “mini-circuits” with or without cardiotomy- and/or venous reservoirs, or downsizing existing, conventional CPB circuits, are hot issues. Downsizing can be accomplished by optimizing all CPB components, including pumps, oxygenator/heat exchanger units, filters, reservoirs, tubing and/or cannulas. With regard to the latter, small cannulas insufficiently support venous drainage by gravity alone, and therefore different strategies have been developed to facilitate venous drainage via such cannulas. These are vacuum-, kinetic- or roller-pump-assisted venous drainage. Despite the fact that these technologies are effective in active venous blood drainage, they are more expensive, and they all increase the risk of micro- or macroemboli in the systemic circulation. To which extent there is really a clinical benefit of minimized CPB-systems, however, is uncertain. Minimized systems are more complicated to handle and can not be used for patients requiring prolonged support with the possibility of unexpected perfusion-related problems. Advantages must be balanced against potential hazards very carefully.\(^{26}\)

As a consequence of improved myocardial protection, operative mortality and morbidity, in particular the low output syndrome, have diminished. There are several variables with regard to cardioplegia: temperature and composition of cardioplegia, the mode (antegrade and/or retrograde) of delivery, and the frequency of administration and the use of terminal warm cardioplegia.\(^{27}\) In the Netherlands, still different kinds of myocardial protection techniques are applied, thus reflecting that there is no consensus which technique is the best.\(^{28}\)
Chapter 1

Although coatings have improved the biocompatibility of extracorporeal circuits, it is still unclear whether or not these improvements have significantly contributed to relevant postoperative clinical benefits.29-33

It is generally accepted, that fast rewarming and hyperthermia of patients during CPB is dangerous. Still, it is unclear to which extent postoperative recovery is affected by the body temperature management during bypass. For examples, it is questionable what the most optimal body temperature is during bypass, and how the postoperative recovery of patients is affected by deep hypothermia.34-37

Leukocyte activation is an important factor of the systemic inflammatory response to CPB. Several strategies have been developed to reduce leukocyte activation and its deleterious effects on postoperative organ function. Despite the fact that leukocyte filtration has been used since the mid-1990s, its efficacy in attenuating the effects of the inflammatory response is doubtful, and its clinical relevance therefore still remains controversial.38,39

At present, CPB remains the key technology allowing more complex cardio-thoracic surgery. The part of today’s CPB circuit that causes most concern is retransfusion of wound blood.40 Also it is still generally accepted that CPB is associated with cognitive changes postoperatively. Current literature on these issues is controversial and consensus is lacking.

Aim and structure of the thesis

In this thesis, we studied blood activation and cognitive function during and after open-heart surgery assisted by CPB. In Chapter 2, we studied the effects of surface modifications of the oxygenator on adhesion of activated platelets, white blood cells and fibrin. In addition, we determined the relation between perioperative complement activation and the numbers of circulating platelet-derived microparticles (Chapter 3) and the postoperative acute phase response (Chapter 4). The effects of retransfusion of wound blood on systemic complement activation were studied in Chapter 5. Furthermore, in this chapter the presence of complement activation molecules and activated complement components on microparticles during bypass was determined. In Chapter 6, we assessed the contribution of retransfusion of wound blood to systemic coagulation activation, and
in Chapter 7 we determined the ability of a cell saver device to remove cell-derived microparticles from patient blood. Finally, in Chapter 8 the cognitive function was studied in patients undergoing either primary or non-primary CABG, e.g. open-heart surgery such as valve replacement or reconstruction assisted by CPB.
REFERENCES


Chapter 1


General introduction, aim and outline of the thesis


