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

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Chapter 9

General discussion and summary
Chapter 9

Aim of the thesis

In this thesis, we studied blood activation during and after open-heart surgery assisted by CPB. In Chapters 2, 3 and 4 the effects of surface modifications of (components of) the extracorporeal circuit on blood activation and its putative postoperative consequences (Chapter 4) were investigated. In Chapters 5 and 6, we studied blood activation in wound blood and determined the effects of retransfusion on systemic complement activation (Chapter 5) and coagulation activation (Chapter 6). In both chapters, also the presence of cell-derived microparticles was studied in detail, and in Chapter 7 we studied the ability of a cell saver device to remove microparticles from patient blood. In Chapter 8, the cognitive function was studied in patients undergoing either primary or non-primary CABG assisted by CPB.

Complement activation during CPB

In Chapters 3 and 4 we showed that systemic complement activation occurs during CPB. Since wound blood was not retransfused into patients in these studies, systemic complement activation during bypass was likely to be due to the contact of blood with the surface of the extracorporeal circuit. This was confirmed by our finding that coating of the oxygenator significantly reduced systemic complement activation. Moreover, although concurrently collected wound blood showed increased complement activation compared to systemic blood (Chapter 5), retransfusion of wound blood failed to trigger additional systemic complement activation. Although surface modification of the extracorporeal circuit significantly reduced systemic complement activation (Chapters 3 and 4), the postoperative acute phase response was unaffected (Chapter 4).

Previously, Sims et al.\textsuperscript{1} showed that complement activation results in the release of microparticles from the surface of platelets and endothelial cells in vitro. It is unknown, however, whether complement activation contributes to the release of microparticles in vivo. Since we found systemic complement activation was affected by surface modification of the extracorporeal circuit (Chapter 3), we determined the occurrence of platelet-derived microparticles under these conditions. Despite the different levels of systemic complement activation, however, the numbers of circulating platelet-derived microparticles were comparable and apparently unaffected by surface modification. Thus,
microparticle formation seems not to be affected by complement activation under these circumstances. On the other hand, we can not exclude that clearance of microparticles, as shown in Chapter 6, may affect the interpretation of these results.

In Chapter 5, also the presence of complement activator molecules and activated complement components was studied. We found that compared to systemic blood, wound blood contains increased numbers of microparticles exposing the activated complement components C1q, C4 and C3. In systemic blood, microparticle-exposed C-reactive protein (CRP) was associated with C1q, C4 and C3. In contrast, in wound blood not CRP but serum amyloid P component (SAP) was associated with C1q, C4 and C3. For comparison, also in systemic blood of patients suffering from rheumatoid arthritis we found an association between microparticle-exposed CRP and C1q, C4 and C3, suggesting that this association is not restricted to patients undergoing cardiac surgery.2

Coagulation activation during CPB

Despite many improvements of the extracorporeal circuit and the use of heparin as an anticoagulant, systemic coagulation activation is still observed during bypass.3,4 In Chapter 2 we found a similar initial adhesion of thrombotic components to non-coated as well coated surfaces under conditions of full systemic heparinization. Persistent attachment of cells seemed to be reduced by surface modification, possibly preventing accumulation of thrombotic elements and propagation of coagulation.

Compared to systemic coagulation activation, coagulation activation in wound blood is much more pronounced.3,5-7 It is generally accepted that retransfusion of wound blood into the circulation contributes to systemic coagulation activation during bypass.8-10

In Chapter 6, we showed excessive coagulation activation in wound blood compared to systemic blood. In addition, we found an increase in systemic coagulation activation, as reflected by increased levels of prothrombin fragment F1+2 despite heparinization, during the time course of CPB. In this chapter, we demonstrated that no systemic coagulation activation occurs when wound blood is discarded, suggesting that retransfusion of wound blood causes the observed increase in systemic coagulation activation. Moreover, these data also indicate that the contact between systemic blood and the surface of the extracorporeal circuit does not activate the systemic coagulation. In addition, we
calculated the *expected* systemic increase in the level of prothrombin fragment F$_{1+2}$, a marker of the in vivo coagulation activation status, upon retransfusion of wound blood. We showed that the *observed* systemic increase of F$_{1+2}$ could be predicted based on the amount of F$_{1+2}$ that was present already in the pericardial blood. Thus, the *observed* systemic coagulation “activation” during bypass is not due to “de novo” coagulation activation, but is caused by dilution of pericardial blood.

**Retransfusion of wound blood: good or bad?**

Throughout the literature, there is discussion with regard to advantages and disadvantages of retransfusion of pericardial blood. Retransfusion of cardiotomy suction blood in patients undergoing CPB has been associated with neurological injury, increased postoperative blood loss, and activation of the coagulation- , fibrinolytic- and inflammatory cascades.\textsuperscript{3,5,6,8,11} Moreover, recently, in an evidence-based review on CPB practice it was concluded that retransfusion of unprocessed cardiotomy blood should be avoided (Class I recommendation, Level B of evidence),\textsuperscript{12} and that blood cell processing and secondary filtration can be considered to decrease the deleterious effects of reinfused shed blood (Class IIB, Level B).\textsuperscript{8} In marked contrast to the before mentioned studies and guidelines, however, Flom-Halvorson et al.\textsuperscript{7} was unable to find any harmful effects of retransfusion of unprocessed wound blood on clinical outcome in almost 5,000 patients. In addition, Rubens et al.\textsuperscript{13}, who treated patients according the before mentioned guidelines, showed that patients undergoing cardiac surgery who received unprocessed wound blood maintained a postoperative cognitive function similar to patients receiving wound blood processed by a cell saver combined with a leukoreduction filter. Patients in the first mentioned group, however, used significantly less blood products. Therefore, from that study it was concluded that retransfusion of unprocessed wound blood is safe.

In this thesis, we found neither additional systemic complement activation nor de novo systemic coagulation activation after retransfusion of pericardial blood (Chapters 5 and 6, respectively). In addition, we observed improved postoperative cognitive function test scores in patients who received retransfused wound blood during bypass (Chapter 8). Therefore, retransfusion of autologous wound blood does not seem to be disadvantageous to patients. We did not anticipate our before mentioned results. Previously, we
demonstrated that pericardial blood contains elevated numbers of cell-derived microparticles, which are strongly coagulant in vitro and in vivo. Therefore, one would expect that retransfusion triggers extensive (systemic) coagulation activation. As shown in Chapter 6, however, microparticles were efficiently cleared from the circulation, thereby reducing the risk of adverse effects such as thrombosis. Although we showed in Chapter 7 that treating wound blood with a cell saver device efficiently removes microparticles, one may wonder whether such treatment is essential to improve patient outcome.

Postoperative cognitive function

In general, the assessment of cognitive function is highly complex due to methodological problems, such as a multitude of applied definitions of cognitive decline, a large number of different existing neuropsychological tests to assess the various cognitive domains, the variety of interval between operation and administration of the neuropsychological tests (range from a few days to several years), data interpretation, statistics, inclusion of a control group, etc. We demonstrated (Chapter 8), in contrast to most of the literature, that postoperative cognitive function improves, even in patients who underwent relatively complex and long cardiac surgical procedures. As shown in various other chapters in this thesis and by studies of various before mentioned investigators, activation of blood upon contact with the extracorporeal circuit of the new generation of heart-lung machines or upon retransfusion of wound blood seems relatively modest. Furthermore, the clinical consequences of blood activation during cardiac surgery are well tolerated by patients. Taken together, we postulate that careful and detailed analysis of postoperative cognitive function may prove that cardiac surgery assisted by CPB is not necessarily detrimental to patients.

Clinical relevance

Taken together, our findings show that blood activation during nowadays cardiac surgery assisted by CPB, whether due to contact of blood with the extracorporeal circuit or by retransfusion of pericardial blood, is much less than generally accepted. As a consequence, also adverse effects such as postoperative cognitive deficits that have historically been associated with this type of surgery are less severe than generally
believed. Based on data presented in this thesis, we believe that cardiac surgery assisted by CPB is a reliable, safe and validated procedure to improve and recover cardiac function.

Considerations of science, evidence, and future directions

The presented body of research in this thesis has raised more questions than providing answers. Many, especially ‘negative’, conclusions were unanticipated and initially perceived as disappointing. We have to admit that we had to a certain degree a positive publication bias before we started our research. We expected to corroborate existing findings and novel aspects, based on our belief in progress of technology. Today, we must conclude that our observations, even in view of explanations, do not yield additional evidence for established scientific concepts and that the step of validation of observations in different settings remains mandatory. In a positive way, one may say that the role of applied science is not simply to copy but also to question already proven innovation.

How could this happen? It is true that a negative publication bias, in the sense that unanticipated results make bad news, creates a selective pressure on positive scientific news in the journals. The fact that this thesis contains chapters that basically represent negative outcome and rejection of assumed technical progress, contradicts the hypothesis of publication bias. Much of the research on devices and technology, however, is industry sponsored. Whether or not established in an official agreement, industrial contract research creates obligations for the researcher. Many deals contain a clause of prepublication reading by the sponsor. Refraining from self-censorship might be punished by rejection of a grant application for industrial funding of a future project.

Publications in peer-reviewed journals much resemble scientific articles in newspapers. This is not a problem but the reader should be able to distinguish which publications truly enrich evidence. Thus, not only challenging science on developing and implementation of technology by new research, but also critically reviewing publications on outcome are the pillars of clinical science in perfusion technology.

The chapters present rather small numbers of patients and investigated samples. One may conclude that small numbers are able to challenge conclusions that are presented as truth or evidence. Thus, the advantage of small-scale research is that it may confirm and
reinforce existing evidence (what is to be expected) or that it may question its validity. This illustrates the often proclaimed dictum in The Netherlands: "small is beautiful" (and cheaper!). It is easier to conduct a small critical study than a big constructive one, for example by means of a randomized controlled multi-centre trial.

Regarding perfusion technology, many device studies are initially small scale and created to confirm the engineering hypothesis and to generate data to support the marketing system. It is obvious, however, that they should be followed by large prospective studies to create sound evidence and a solid basis for scientific progress. Much device research money is wasted by duplicating small scale studies focussing on details with little clinical relevance in stead of large scale research.

This thesis raises questions about the potential to improve the quality of the current state-of-the-art heart-lung machines. Without special-focus improvements, cardiopulmonary bypass is effective and safe. Assumed dangers, such as recirculation of filtered wound blood, could not be substantiated in this research. On the other hand, one should keep in mind that progress in biocompatibility does not automatically generate improved patient safety. New technology can be complex and difficult to handle and eventual benefits can be questionable.

Open-heart surgery is a complex, risky, and multidisciplinary endeavour. I hypothesize that optimization of team work at the current state of technology may create more benefits to patients than improvement of perfusion device technology.
REFERENCES


