SUMMARY

With the development of open heart surgery in the last decades the life expectance and the quality of life of patients with congenital or aquired heart diseases improved substantially. However, all patients are still at risk for a post perfusion syndrome (PPS), due to a whole body inflammatory reaction induced by the blood surface interaction of the extracorporeal circuit. By the blood surface interaction the contact and complement system are activated. Contact system activation is related with the impaired hemostasis during and after cardiopulmonary bypass (CPB), whereas the activation of the complement system correlates with the organ dysfunction following CPB. Although the recent use of protease inhibitors reduced the activation of the contact system and consequently preserved hemostasis, no reduction of complement activation nor in organ dysfunction has been observed.

Since complement activation is particularly seen after reperfusion of the heart and lungs at the completion of the cardiac correction, we considered blood activation by a process *in*dependent of the blood surface interaction. This thesis evaluates the material *in*dependent blood activation during CPB and the role of this activation process on the development of the post perfusion syndrome. We especially investigated the release of endotoxin, its effect on the whole body inflammatory reaction and the protective effect of corticosteroids on this reaction.

Chapter 1 is a general introduction to this thesis, describing and specifying the targets of the problems. In addenda I, II and III a more detailed description is given of the post perfusion syndrome, the complement system and endotoxin in relation to open heart surgery.

To clarify if endotoxin could contribute to the development of the whole body inflammatory reaction the time relation of release of endotoxin into the systemic circulation and its activation process during CPB was investigated in a prospective study on patients undergoing CPB (**chapter 2**). We found significant increases of endotoxin concentration after start of bypass and after release of the aortic cross-clamp, accompagnied by an immediate increase in complement activation (C3a) and the formation of tumor necrosis factor (TNF) later on. Since TNF is a more potent mediator of organ dysfunction and endothelial injury than the complement factor C3a by itself, we concluded that endotoxin may play a pivotal role in the generation of the whole body inflammatory reaction.

In a placebo controlled double blind study on patients undergoing CPB, the treatment of dexamethasone on the material *in*dependent blood activation and on the development of the post perfusion syndrome following CPB was investigated (**chapter 3**). We showed a strong leukocyte inflammatory reaction upon release of the aortic cross-clamp of which particulary the TNF formation correlated with the hemodynamic instability seen in the post operative period. Prophylactic dexamethasone treatment (1 mg/kgbw) inhibited the leukocyte inflammatory reaction of this material *in*dependent blood activation effectively and prevented the post

perfusion phenomena, while no inhibition of complement activation during CPB was observed. Therefore it could be concluded that the material *in*dependent blood activation, seen after release of the aortic cross-clamp, is the main mediator in the development of the post perfusion syndrome and not the material dependent activation induced by the surface of the extracorporeal circuit.

To determine if other corticosteroid regimens could also have an inhibitory effect on the material *in*dependent blood activation process during CPB, we investigated the effects of three - most frequently used - corticosteroid regimens during CPB, in a placebo controlled double blind clinical study (**chapter 4**). A high dose corticosteroid treatment was the most effective in inhibiting the material *in*dependent activation, especially dexamethasone in a dose of 1 mg/kgbw, more than methylprednisolone (30 mg/kgbw). A low dose corticosteroid treatment (prednisolone 1 mg/kgbw) was less effective because of a short duration of action. None of the corticosteroid regimens had any effect on the material dependent blood activation.

To determine the effects of endotoxin on the activation of blood cells and plasmatic systems in more detail and to investigate the protective effects of corticosteroids on this process, studies were performed in rabbits.

In **chapter 5** we showed that the activation of blood cells, complement, arachidonic acid and fibrinolytic systems, seen after a short endotoxin infusion, corresponded with the activation seen after release of the aortic cross-clamp in patients undergoing CPB. All rabbits died upon the endotoxin infusion after about 48 hours. This study showed that endotoxin is indeed a strong activator of blood cells and plasmatic systems with deleterious effects and therefore can contribute to a whole body inflammatory reaction.

In **chapter 6** we investigated if corticosteroids could prevent the activation process and deleterious effects of endotoxin in rabbits. The effects of a prophylactic low and high dose methylprednisolone treatment were evaluated, to determine if a low dose corticosteroid treatment with less side effects could be as effective as a high dose. Both corticosteroid treatments were not able to inhibit the complement activation, but both effectively inhibited the activation of leukocytes, platelets and their release products and prevented death of all animals. So prophylactic corticosteroid treatment, both a low and a high dose, prevents the deleterious effects of endotoxemia and supports the beneficial effects of corticosteroid treatment on the material *in*dependent activation observed in patients undergoing CPB.

We evaluated in **chapter 7** the effect of corticosteroid treatment on complement induced white blood cell and platelet aggregation, as is known to occur by complement activation during CPB. Complement activated plasma and serum were infused in rabbits, prophylacticaly treated with a high dose methylprednisolone or a placebo. We showed that high dose methylprednisolone treatment was able to inhibit in serum the complement induced blood cell aggregation, but not in plasma. We concluded therefore that corticosteroids are not able *in vivo* to inhibit comple-

ment induced blood cell aggregation and that other simultaneously activated plasmatic components, such as fibrin monomers, play a role in blood cell aggregation.

In an epilogue (**chapter 8**) the role of the material *in*dependent blood activation on the development of the whole body inflammatory reaction is described. The release of endotoxin into the systemic circulation, especially by the formation of TNF, can be responsible for the adverse effects in CPB. Therefore it is important to focus on the endotoxin release to improve the clinical course following CPB. We describe the possibilities of preventing systemic endotoxemia and treatment of endotoxemia in patients undergoing CPB.

Conclusion

We demonstrated a significant increase in endotoxin concentration during CPB, causing a material *in*dependent blood activation with a strong leukocyte inflammatory reaction. Especially the formation of TNF by endotoxin correlated with the hemodynamic instabillity seen in the post operative period. Corticosteroid treatment could inhibit the leukocyte inflammatory reaction, including the TNF formation, and so prevented the hemodynamic instability after CPB in a dose dependent way. In the animal studies we could mimic these effects of endotoxin and the protective effects of corticosteroid treatment. Furthermore we demonstrated that complement activation, induced by blood surface interaction, could not be inhibited by corticosteroids. We therefore postulate that the material *in*dependent blood activation is the main mediator in the development of the post perfusion syndrome instead of the material dependent blood activation. Therefore attention has to be focussed on the inhibition and/or prevention of the material *in*dependent blood activation during CPB, and especially on the endotoxin release.