8. Summary

"Influence of different concepts of heparinisation on function and stability of the isolated hemoperfused porcine jejunum: establishing a new model"

Isolated organ perfusion offers, as a supplementary method to animal experiments, a very good prerequisite for a better study of the important fields of pharmacology and toxicology and of intensive care and transplantation medicine.

Breakdown of the barrier function, following bacterial translocation, is an important motor for the development of sepsis. *In vivo* complexity often hampers the identification of a particular pathophysiological mechanism triggered by the organ itself. Thus, we established a hemoperfused *in vitro* system giving access to investigations on intestinal function.

Since activation of coagulation of the blood is an important aspect in research on extracorporeal circuits we investigated different heparinisation concepts, with respect to both functionality and stability of the system.

In four groups isolated normothermic hemoperfusion of 18 porcine jejunal segments was performed over three hours. Organs were taken from pigs of mixed DL*PI (42 ± 5kg; MEAN ± SD). Jejunal segments with an average weight of 191 ± 40 g (MEAN ± SD) were taken out under general anaesthesia. Isolating different organs the animals were sacrified by final exsanguinations during the blood harvesting procedure (Project: O 0049/99). Therefore, the maintenance of organ function and sensitivity of coagulation on the one hand and the function of the capillary dialyse module used for gas exchange on the other hand should be established under *in vitro* conditions.

Statistical analysis was performed using non-parametrical tests: for inter-group analyses Mann-Whitney-U test and for intra-group analyses the Wilcoxon test.

Depending on the group anticoagulation with unfractionated heparin was performed in 2 vs. 3 steps: 1. animal, 2. blood reservoir, 3. with (w) or without (w/o) priming (P) of the perfusion circuit. Heparin doses in the blood reservoir were differentiated between high (Hi) vs. low (Lo) concentrations.

Total heparin doses, including the animal, given in I.E.: group 1: 15.750 ± 500 (HiHep w/oP), group 2: 6.375 ± 679 (LoHep w/oP), group 3: 10.904 ± 413 (LoHep wP) and group 4 11.300 ± 200 (LoHep wP wCd).

For studying the functionality and stability of the system hemodynamic, haematologic and chemical parameters as well as functional and anticoagulation parameters have been evaluated. Furthermore, histological samples were taken before and after perfusion.

Group 1 (HiHep w/oP) showed massive bleeding on the mucosa, whereas the jejunal segments of the low heparinised groups (LoHep) showed only partial light bleeding.

Aim of the study was to achieve a constant mean arterial pressure over the arterial flow. Hereby, group 2 (LoHep w/oP) showed high fluctuations. This group (LoHep w/oP) had up to 75 % higher perfusion resistance (*$p<0.05$) compared to groups 1 (HiHep w/oP), 3 (LoHep wP) and 4 (LoHep wP wCd). A significantly higher oxygen consumption was found in group 3 (median between 113.2 and 156.6 µmol/min*100 g) and respectively, during the first two hours, in group 4 (median of 94.3 and 114.2 µmol/min*100 g) compared to group 2 (median beetween 50.6 and 71.8 µmol/min*100 g). These groups also showed significant glucose absorption, low lactic acid production as well as stable gut motility.

Group 2 (LoHep w/oP) was characterised by a tendency for activated thromboplastin time and constant decrease in fibrinogen and antithrombin-III-concentrations and a constant increase of the d-dimere. This group also showed a significant decrease in leukocytes and a slight decrease in thrombocytes.

Group 3 (LoHep wP), in contrast, showed almost stable values of the coagulation pattern and of the concentration of leukocytes and thrombocytes. Thereby, group 3 (LoHep wP) provided stable perfusion conditions, and a still maintained best functional capacity. The heparinisation concept of this group showed specifically fundamental influences on in vitro viability of the small intestine. Adding cadmium to the ingesta the concentration raised up to 35.4 µg/l (difference of the median) in the blood.

The model of isolated hemoperfused jejunum is giving a most promising option to study the absorption of toxic substances on the one hand and to answer questions of intensive care and transplantation medicine on the other hand.