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**Beneficial effects of carbon monoxide releasing molecules in
inflammation and intimal hyperplasia**

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CO releasing molecules (CORM-3) are a novel class of compounds that release CO in a controllable fashion. We investigated the beneficial effect of CORM-3 in cold preservation and its anti-inflammatory effect on vascular endothelial cells.

In the first part of this study, the beneficial effect of CORM-3 on hypothermia-induced injury in HUVECs was investigated and its influence on vascular remodelling and vascular function after syngeneic rat aorta transplantation. Both in vitro and vivo CORM-3 protected endothelial cells against hyperthermia-mediated injury. Cold storage induced endothelial denudation and intercellular gap formation in isolated rat abdominal aortas and resulted in an impaired vascular function. The latter was largely due to impairment of endothelial mediated NO production. Addition of CORM-3 to the preservation solution prevented endothelial denudation and improved vascular function. Two months after aorta transplantation in syngeneic rats, neo-intima was significantly increased in aortas that were subjected to 24 hrs of cold preservation, but not in transplanted aortas that were preserved in the presence of CORM-3.

In the second part of this thesis, we studied how CORM-3 modulates the expression of adhesion molecules on endothelial cells stimulated by TNF- α and whether the expression of HO-1 contributes to the modulation. Our results showed that CORM-3 consistently inhibited the up-regulation of VCAM-1 and E-selectin in TNF- α stimulated HUVEC, partly due to the deactivation of NF κ B. Interestingly, down-regulation of VCAM-1 and E-selectin expression by CORM-3 occurred even when CORM-3 was added 24 hrs after TNF- α stimulation. Sustained expression of VCAM-1 required the continuous presence of TNF- α . TNF- α removal was more effective in reducing VCAM-1 mRNA, but VCAM-1 protein was down-regulated more rapidly when CORM-3 was added compared to TNF- α removal. This suggests the involvement of post-transcriptional regulation of VCAM-1 by CORM-3. Although CORM-3 up-regulated HO-1 in a Nrf2 dependent fashion, HO-1 did not significantly contribute to the effect by CORM-3. Neither in HO-1- nor in Nrf2-siRNA treated HUVEC the efficacy of CORM-3 to down-regulate VCAM-1 expression was lost.