Uremia-induced effects on cardioregulatory mechanisms in the context of the cardiorenal syndrome

Summary

Various cardiorenal mouse models have been presented in literature, although with variable outcomes and reporting of highly varying parameters, thus not allowing a direct comparison of the different models. Accordingly, this thesis aimed to perform a comprehensive and standardized characterization and comparison of different mouse models of chronic kidney disease (CKD) to examine the suitability of a mouse model to mirror the clinical situation of a CKD patient developing uremic cardiomyopathy.

CKD was induced by either 5/6 nephrectomy (Nx) or an adenine-supplemented diet in three different mouse strains (C57BL/6J mice, hyperlipidemic C57BL/6J *ApoE*$^{-/-}$ mice, 129/Sv). Characterization of the mouse models was performed by analyzing kidney function and morphology, blood pressure as well as heart function, cardiac hypertrophy and fibrosis, calcification and inflammation as well as oxidative stress.

C57BL/6J mice (Model 1) as well as C57BL/6J *ApoE*$^{-/-}$ mice (Model 2) developed only a mild degree of kidney damage upon 10 weeks of 5/6 Nx, without prominent effects on heart function or cardiac molecular changes. Feeding C57BL/6J mice a low adenine diet (Model 3) did not result in sufficient kidney dysfunction after 6 weeks nor in clear cardiac dysfunction, except for a slightly reduced ejection fraction.

In contrast, CKD-induction by high concentrated adenine diet in hyperlipidemic C57BL/6J *ApoE*$^{-/-}$ mice resulted in a stable, moderate kidney dysfunction (Model 4). Although no effects on heart function or cardiac morphology were observed, increased oxidative stress markers were detected in cardiac tissue from CKD mice. This was also observed in 129/Sv mice with a prolonged moderate to severe kidney damage induced by adenine diet over 13 weeks (Model 5). The latter was accompanied by activation of oxidative stress signaling but also by anti-inflammatory feedback responses as revealed by additional RNA sequencing, pointing to imbalances of inflammatory and oxidative stress responses in the heart in the context of at least moderate CKD.

Overall, this thesis demonstrates that the development of a cardiorenal mouse model with a clear dysfunctional cardiac phenotype as observed in CKD patients is still challenging. Nonetheless, this study considerable advances the knowledge in cardiorenal research by providing a detailed, standardized comparison of different cardiorenal models, as well as by revealing that at least a moderate state of CKD results in increased oxidative stress markers in the heart.