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

7. Societal Impact

Cardiovascular diseases (CVD) are the leading cause of death worldwide. CVD accounted for about 31 % of global deaths in 2019. Moreover, the prevalence of chronic kidney disease (CKD) is rising worldwide. In the past years, there is increasing evidence that CKD is an independent risk factor for the development and progression of CVD, since about 50 % of CKD stage 4-5 patients suffer also from CVD. The CVD mortality rate in those patients is about 40-50 % compared with a 26 % CVD mortality rate in patients without CKD. The pathophysiological link between CVD and CKD is called the cardiorenal syndrome.

One major cardiac pathology occurring in CKD patients is the pathology termed as uremic cardiomyopathy. The underlying mechanisms are not completely understood yet, which complicates the precise treatment of the disease. A necessary approach to examine the underlying mechanisms of an organ crosstalk like the cardiorenal syndrome is the investigation in animal models. In literature different mouse models in the field of cardiorenal research were presented, with all reporting on highly variable parameters which highly complicates a comparison of those different mouse models.

Thus, a clear comprehensive and standardized characterization and comparison is of great importance to find a suitable cardiorenal mouse model for unravelling underlying mechanisms of uremic cardiomyopathy, and is presented in this thesis.

This study brought light into the jungle of cardiorenal mouse models. The cardiac analysis of five different mouse models revealed that at least a moderate CKD results in increased oxidative stress in hearts of CKD mice, although neither the heart function nor cardiac morphological remodeling was affected. On molecular level it was revealed that not only oxidative stress signaling is affected by CKD, but also protective feedback responses are upregulated in the heart. Future studies should address whether the increased oxidative stress is a maladaptive predisposition or a protective conditioning for subsequent cardiovascular damage. Furthermore, this study revealed that the mere induction of CKD not necessarily results in a clear cardiac functional phenotype and thus raises questions about a simple “single-hit” concept of uremic cardiomyopathy.

This leads to the suggestion that a further stressor is needed, as for example an additional cardiovascular risk factor or further cardiovascular injury, such as pressure overload, as often found in CKD patients.

The comprehensive standardized characterization and comparison of five different cardiorenal mouse models in this study enlightened unclarities about the use of mouse models in the field of cardiorenal research by using different mouse strains and different CKD induction methods. Furthermore, it raises awareness for reporting a broader set of parameters of kidney and heart function and remodeling processes in cardiorenal research instead of focusing on highly selected processes, this also to avoid unnecessarily repetition of mouse experiments which may not lead to the desired outcome.

The insights resulting from this thesis were shared with the scientific community as well as with the general public by publication in scientific journals as well as poster and oral presentations.