Increased cardiovascular risk in patients with chronic kidney disease

Summary

This doctoral thesis is composed of two results parts that deal with different aspects of the background of cardiovascular problems in patients with chronic kidney disease (CKD).

First, a focus was set on the identification of substances that are elevated in CKD patients and impair the function of cardiomyocytes. For this purpose, hemodialysate from CKD patients was fractionated by chromatography with each fraction screened for adverse effects on cardiomyocyte metabolic activity. A drug metabolite was identified by mass spectrometry in fractions that reduced the metabolic activity of cardiomyocytes. This metabolite could be confirmed to negatively affect cardiomyocytes at doses detected in CKD patients treated with this drug. Since the drug metabolite especially accumulates in patients with advanced CKD due to reduced renal clearance, the identification of it as potentially damaging to the heart may have a decisive influence on the therapy of dialysis patients in the future.

The second part aimed to investigate the effect of CKD on the heart after myocardial infarction in an animal model. Reduced cardiac contractility and relaxation ability was observed in CKD compared to non-CKD animals after infarction, in line with clinical observations. Using a combination of flow cytometry analyses of leukocytes, RNA sequencing and array-based kinase activity screening in heart tissue post-infarction, alterations in inflammatory cell mobilization and phenotype as well as potential candidate mediators of deteriorated heart function could be identified.

Overall, this thesis sheds further light on pathophysiological mechanisms of CKD associated cardiovascular disease, identifying new candidate targets for intervention in this comorbidity.