Increased cardiovascular risk in patients with chronic kidney disease

7 Societal impact

Cardiovascular disease accounts for one third of deaths, making it the leading cause of death worldwide [3]. However, CKD as a cause of death is also on the rise and is now the 10th most common cause of death. The interaction of the diseased kidney and heart is called the “cardiorenal syndrome”. About 50% of CKD patients at stage 4-5 also suffer additionally from CVD. In CKD patients, the mortality rate after a cardiovascular event is 40-50%, twice as high as in non-CKD patients [30, 31]. So far, however, the underlying mechanisms are only incompletely understood.

Due to the reduced filtration capacity of the kidneys, many substances accumulate in the blood of CKD patients that are excreted under healthy conditions. Some of these substances have a toxic effect and have been linked in various ways to cardiovascular complications. However, the list of uremic retention compounds accumulating in the circulation of CKD patients and contributing to increased cardiovascular risk is potentially incomplete and requires further study.

The first result part (*Chapter 3*) of this thesis identified a specific metabolite in hemodialysate of CKD patients negatively affecting cardiomyocyte health. The metabolite is assigned to a drug used for immunosuppression in patients in preparation for solid organ transplantation. This again shows that the treatment of CKD patients should be selected with caution in order to prevent unwanted side-effects in relation to the cardiovascular system. My findings will trigger in-depth follow-up research e.g. in animal experiments and mechanistical *in vitro* studies to provide further insights.

The rate of cardiovascular events is not only increased in CKD conditions, but also the mortality after MI increases in CKD patients. Furthermore, the incidence of heart failure

post MI increases. Up to now, no all-encompassing treatment option targeting the different types of accumulated metabolic uremic retention compounds has been developed that improves the poor quality of life and high mortality of these patients with post-MI heart failure because of incomplete information about underlying mechanisms.

In the second result part of this thesis (*Chapter 4*), different screening methods were used to identify potential mediators reducing cardiac function in CKD post MI, leading to the identification of dysregulated molecular mediators with known roles in cardiomyocyte dysfunction. These findings will now stimulate further studies to address whether the identified molecular mediators also contribute on functional level to impaired cardiac contractility in CKD after MI. Overall, the findings in this thesis contribute to a better understanding of the underlying mechanisms of reduced heart function post MI, thereby contributing to better and specialized treatment options in future.

In summary, this thesis addressed metabolic changes in CKD patients in relation to their increased cardiovascular risk. It revealed that I) metabolites of drugs, which are in healthy conditions not a problem, can have a severe impact in terms of cardiomyocyte damage due to increased accumulation in CKD conditions; and II) specific molecular mediators with known role in cardiac dysfunction are upregulated in the infarcted heart in CKD conditions. **In this way, this thesis eventually will contribute to a better diagnosis, characterization and treatment of heart failure post-MI in CKD patients in the future.**