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Reversing the reno-cardiac perspective

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Chapter VII

General Discussion

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The reno-cardiac perspective

The present thesis explored the relationship between renal and cardiovascular function. Within the reno-cardiac perspective, it had already been shown that an independent and graded association exists between renal dysfunction and the occurrence of cardiovascular morbidity and mortality in patients with hypertension as well as in subjects derived from the general population [1;2]. In patients with type 2 diabetes it was also shown that concurrent renal dysfunction increases cardiovascular risk [3-9]. However, patients with relatively normal renal function as well as those with severe renal dysfunction including dialysis often have been excluded from intervention studies aimed at documenting cardiovascular risk reduction in diabetic patients. We therefore analyzed the risk for cardiovascular events in a large cohort of type 2 diabetic patients with hypertension across all stages of renal function, including patients with apparently normal renal function. The combined outcome analyses of the LIFE and RENAAL studies showed a progressively increasing risk for cardiovascular complications across the entire range of incremental baseline serum creatinine, which underlined the value of serum creatinine measurements to assess both renal and cardiovascular risk. There appeared to be no serum creatinine threshold level for this increased cardiovascular risk. Altogether, it can be concluded that renal dysfunction represents a key risk factor for cardiovascular complications across important populations.

At present, no definite explanation can be given for the progressively increasing cardiovascular risk in patients with renal dysfunction. This limitation also applies to our analyses, since both the RENAAL and LIFE studies were primarily clinical outcome studies, not mechanistic studies. The limited spectrum of physiological parameters obtained did not allow for a detailed functional analysis between renal function and cardiovascular risk. Although the mechanisms underlying an independently increased risk in patients with increasing renal dysfunction are not fully understood, multiple explanations have been postulated. As mentioned earlier, previous studies have indicated that renal dysfunction is associated with increased levels of inflammatory factors, left ventricular hypertrophy, abnormal apolipoprotein levels, elevated plasma homocysteine, enhanced coagulability, anemia, increased arterial calcification, endothelial dysfunction, arterial stiffness, renin-angiotensin-system (RAS) activation and sympathetic overactivity [10-18]. The way these and other factors may interact to increase the risk of adverse cardiovascular outcomes remains unclear, but finding a common denominator would constitute a major advance in the quest for more effective and targeted treatment of patients at risk. The fact that both myocardial infarction and stroke contributed to the overall composite outcome in our analyses point towards generalized vascular pathophysiological mechanisms driven or influenced by the extent of renal function loss. In this respect, it is important to emphasize that inhibition of the

RAS can improve both cardiovascular and renal outcome in type 2 diabetic patients with hypertension [19], which may be particularly relevant for those with more severe renal dysfunction [20]. Overall, there remains a need to further explore the relationship of renal function and increased cardiovascular risk, particularly in functional terms.

The cardio-renal perspective

In contrast to this focus on further exploring the reno-cardiac perspective in the last decades, substantially less attention has been paid to the investigation of a potential reverse relationship, *i.e.*, the effects of cardiac dysfunction on the course of renal function. This may have been caused by the remarkably high level of cardiovascular morbidity and mortality in patients at the more severe stages of renal dysfunction [21;22], resulting in a rather unidirectional point of view. We therefore aimed to reverse this perspective and also questioned whether cardiac dysfunction could affect renal outcome. A proof-of-concept study was performed in an effort to conclusively elucidate the presence of a cardiac effect on a chronic state of mild renal dysfunction. In a four-arm surgical intervention study, we showed that myocardial infarction aggravated the mild state of chronic renal damage in unilateral nephrectomized rats as evidenced by the enhanced progression of proteinuria and focal glomerulosclerosis. Interestingly, this effect appeared to be dependent on the size of the myocardial infarction. These data are relevant, as the influence of cardiac damage on kidney function has never been thoroughly examined before in an experimental setting.

The data available suggest that cardiac dysfunction influences renal vascular function, which fits into the known classical cardio-renal relationship (fall in cardiac output with eventual fall in glomerular filtration rate). Mento *et al.* [23] found statistically significant reductions in renal blood flow, one month after induction of myocardial infarction by ligation of the left coronary artery in rats. This post-myocardial infarction intrarenal vasoconstriction contributed to a reduced renal excretory function, which was responsive to RAS modulating pharmacotherapy [23-25]. Less specific to the kidney, several authors have shown that myocardial infarction may result in endothelial dysfunction in both large conduit and resistance arteries in rats [26-31]. The extent of endothelial dysfunction appeared to be related to the size of the myocardial infarction and was preserved by RAS modulating therapy [32-34]. Gschwend *et al.* [35] found a significant inverse correlation between individual renal vascular endothelial function and renal susceptibility to damage in rats by means of 5/6 nephrectomy. When the observations from our study are put into the context of these previous findings, it appears that cardiac, endothelial and renal function are interlinked. One may infer that dysfunction of one of these functions affects the other two components, and that dysfunctional components might even interact in a synergistic way to contribute to the pathogenesis

of 'reno-cardio-vascular' disease. This would mean that when individuals are struck by a myocardial infarction, their risk of more progressive renal function loss increases, rendering them even more vulnerable for subsequent cardiovascular events and thereby closing a vicious circle.

Although our proof-of-concept experimental study was not aimed to investigate the underlying mechanisms, several mechanisms could be hypothesized including hemodynamic alterations, involvement of the RAS and sympathetic nervous system, involvement of the natriuretic peptide system and inflammation. Bongartz *et al.* [36] have previously presented a model in which four components are assumed to establish the connection in a setting of combined cardiac and renal dysfunction, complementary to Guyton's valuable physiological model explaining cardio-renal interaction in terms of extracellular volume, cardiac output, blood pressure and diuresis. A schematic overview of this model is provided in the figure below.
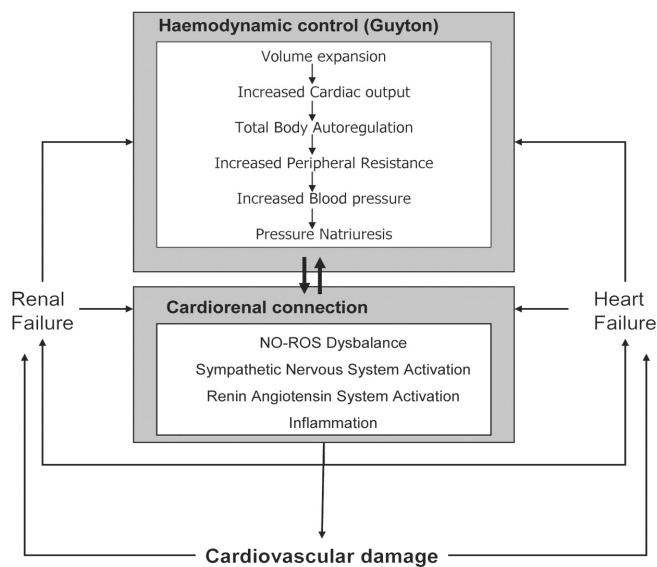
Figure 1. Connection between cardiac and renal dysfunction (L.G. Bongartz *et al.* [36]).

Regarding our experimental model, it could be inferred that a reduced cardiac output after myocardial infarction may lead to reduced renal perfusion, which in turn could lead to compensatory RAS activation. This RAS activation in turn could be detrimental to both heart and kidney. An elevated angiotensin II level is known to interact with cardiac function leading to progressive cardiac function loss [37] and elevated angiotensin

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II levels may also lead to progressive renal damage [38]. Accordingly, RAS-intervention with either an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker can protect both heart and kidney [39;40]. Although controversial, neutral endopeptidase (NEP) inhibition has also been shown to be protective in progressive function loss of either the kidney or the heart [41-44], and the combination of ACE and NEP inhibition (*i.e.*, vasopeptidase inhibition) has been claimed to be more effective in this regard [45-49]. On the basis of these considerations, we designed a follow-up experimental study to investigate the mechanistic involvement of both the RAS and natriuretic peptide system in the experimental cardio-renal model. We showed that the detrimental cardio-renal interaction could be attenuated by treatment with either an ACE-inhibitor or a vasopeptidase inhibitor (VPI). These interventions are of potential clinical relevance since they could retard the vicious circle described above. This will however require changes in prescribing behaviour of physicians treating patients after myocardial infarction. Patients are not regularly prescribed RAS intervention after myocardial infarction [50], while those 'cardiac' patients with compromised renal function are being approached with utmost care as far as RAS intervention is concerned [51]. It should be noted that the study left only little evidence for a discernible beneficial effect of an increased level of natriuretic peptides beyond concurrent RAS inhibition in this cardio-renal model with short-term pharmacological intervention, although this does not exclude VPIs to still have a clinical contribution in patients with renal and cardiac dysfunction. VPIs have shown to be effective in the context of more isolated renal and cardiovascular disease [47;49]. It should also be acknowledged that RAS inhibition is invariably associated with blood pressure reduction. Therefore, lowering blood pressure by means of a calcium channel blocker would be an interesting strategy to further allow for a distinction between blood pressure lowering *per se* and blockade of the RAS in future experiments.

In view of the evidence obtained in this experimental interaction model, it is important to discuss whether a comparable cardio-renal impact exists in humans as well. At present, only very limited data is available regarding cardio-renal interaction in humans. Some clinical findings were derived from the Captopril and Thrombolysis Study, which indicated that renal function declined in a selected population of patients with a previous anterior wall myocardial infarction [52]. However, this study neither examined renal function before myocardial infarction, nor did it include a control group providing comparative data against subjects without such an event. In an effort to further characterize the existence of a cardio-renal impact in humans, we investigated the effect of a first ischemic cardiac event on the course of long-term renal function in the general population on the basis of longitudinal data obtained from the PREVEND study [53;54]. A first ischemic cardiac event appeared to enhance the natural decline in renal function, independent from other risk factors for renal dysfunction. Based on the

pre-clinical experimental finding of an increased level of focal glomerulosclerosis after myocardial infarction, a larger decline in renal function in subjects with a first ischemic cardiac event may reflect this enhanced progression of glomerulosclerosis. This, however, needs further confirmation in the absence of renal biopsies in this population-based study. Overall, these experimental and clinical data highlight the risk for enhanced renal function loss after an ischemic cardiac event. The results should be appreciated in the context of the fact that even mild renal dysfunction is a major cardiovascular risk factor after myocardial infarction [55], thereby closing a vicious circle in humans as well.

Improving clinical outcome

These findings raise the issue which parameters should be targeted to provide effective organ specific protection in patients at high risk for renal adverse events. Although previous studies have indicated that albuminuria is a major renal risk factor in diabetic patients with nephropathy [56-60], the current treatment of hypertensive patients with diabetic nephropathy is commonly targeted to blood pressure only. In a *post-hoc* analysis from the RENAAL study, we showed that changes in albuminuria were not concordant in a substantial proportion of patients when titrated for blood pressure, while the risk for end-stage renal disease showed a clear dependency on albuminuria reduction regardless of the change in blood pressure under treatment. This also applied to the residual level of albuminuria. We therefore concluded that anti-hypertensive treatment aimed at improving renal outcomes in patients with diabetic nephropathy could require a dual strategy, targeting both albuminuria and blood pressure reduction. The exact reason for the association between albuminuria and renal risk remains unclear, but several mechanisms may be involved. First, albuminuria may represent a marker of generalized endothelial dysfunction, which in turn may be influenced by activation of the RAS that has a major role in the development of endothelial dysfunction and atherosclerosis [61;62]. This would be in agreement with results obtained by Ochodnicky *et al.* [63-65] showing that the extent of endothelial dysfunction was a predictor of the susceptibility to renal damage. A complementary mechanism could be that persistent transvascular albumin leakage is involved in chronic low-grade vascular inflammation, leading to organ damage in the long term. Our *post-hoc* observation that changes in albuminuria during treatment translated into changes of renal events is suggestive for but not definite proof of a causal role of albuminuria. Thus, whether albuminuria is a risk marker or a risk factor for cardiovascular disease therefore requires further evaluation in the future, by means of conducting prospective randomized clinical outcome studies with an albuminuria-based titration of pharmacological intervention. Phase III studies addressing the issue of a causal relationship between albuminuria reduction and hard clinical endpoints are currently underway [66].

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In medical practice, the instruments to implement a therapeutic approach with a cardio-renal signature mainly relate to life-style changes (*e.g.* smoking cessation, diet restrictions) and pharmacological intervention. In our investigational programme, we focused on two main intermediate physiological parameters eligible for pharmacological intervention. In line with a RAS intervention-based reduction of blood pressure and albuminuria, novel therapeutic approaches will also be based on these two modifiable risk factors for which causal role in disease progression has been implicated. Several anti-albuminuric and/or RAS blocking compounds such as sulodexide, thromboxane antagonists (*e.g.* picotamide), vasopeptidase inhibitors (*e.g.* AVE7688), and renin inhibitors (*e.g.* aliskiren, remikiren) are currently under study. All of these may have the potential to further improve clinical outcomes in patients with cardiovascular and renal disease, either when used as monotherapy or add-on therapy. In this respect, a gradual shift towards an increased utilization of add-on therapies seems likely in the future, given the natural resistance of blood pressure and albuminuria to pharmacological intervention and a general trend towards lower target levels in clinical practice such as for hypertensive patients with diabetes. The fact that progressively lower levels of albuminuria were shown to be associated with an increased level of cardiovascular risk during the past years [54;67;68], might eventually translate into a recommendation to maximally decrease the level of albuminuria in future guidelines. Therefore, it is no surprise that more and more pharmaceutical companies currently develop fixed combination treatments, despite criticism stating that this pull towards a fixed combination approach has the potential to interfere with the preferred flexible uptitration of individual monocomponents.

Overall, the present thesis further characterized cardio-renal interaction as a two-way process by reversing a predominantly reno-cardiac perspective. A cardiac impact on the course of renal function was evidenced in an experimental as well as a clinical setting, and the mechanistic involvement of both the RAS and natriuretic peptide system were explored. In view of this emerging evidence regarding the presence of cardio-renal interaction, a relevant challenge lies in further unravelling the complex of mechanisms involved in the development and progression of cardio-renal disease. In the past years, the mechanisms postulated have extended beyond the known classical cardio-renal relationship in which cardiac damage causes a fall in cardiac output and eventual fall in glomerular filtration rate. An important mechanism implicated in the genesis of many different aspects of cardiovascular dysfunction in renal patients is endothelial cell dysfunction, which could be a final common pathway resulting from an interplay of several factors. To this end, it has been hypothesized that a complex interplay of the activity of the RAS, chronic inflammation, oxidative stress and the sympathetic nervous system is involved in the development and progression of combined renal and cardiac dysfunction [36]. The characteristics of this cardio-renal connection implicitly suggest that

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current treatment options resulting in inhibition of RAS components or the sympathetic nervous system will not suffice in an effort to prevent the progression of detrimental cardio-renal interaction, underlining the need for the investigation of novel therapeutic options beyond ACE inhibitors, angiotensin II receptor blockers, aldosterone antagonists and beta-blockers. In addition, adverse events such as electrolyte imbalances (*e.g.* hyperkalemia) or symptomatic hypotension may limit the combined use of these agents in vulnerable patients such as the elderly and those with renal dysfunction, diabetes mellitus and/or heart failure. Efficacious and safe therapies to directly influence the level of oxidative stress and inflammation in the setting of cardio-renal disease are currently not available. Although a further exploration of cardio-renal interaction will be difficult, at least it has the prospect of delivering new targets eligible for pharmacological intervention aimed at improving clinical outcomes.

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