

# CHAPTER 8

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General discussion



## General discussion

In the present thesis several aspects of dysfunction of the cardiorenal axis are discussed, mainly focussing on the renin angiotensin system and on elevated urinary albumin excretion. In addition, we provide further evidence that even mild renal dysfunction carries a worse long term prognosis. We demonstrate that elevated urinary albumin excretion (UAE) is a common finding in severe chronic heart failure patients, and that spironolactone use activates a RAS feedback mechanism thus leading to high angiotensin II levels in these patients.

Since blood pressure is an important factor in the pathophysiology of UAE, we used an in vitro model, to evaluate some functional aspects of the AT<sub>2</sub> receptor. The vasoactivity of the AT<sub>2</sub> receptor has been the subject of study in human arteries only once before.<sup>1</sup> Most of the textbooks state that stimulation of the AT<sub>2</sub> receptor opposes the effects of the AT<sub>1</sub> receptor. We demonstrated that the AT<sub>2</sub>R does not mediate vasodilation in human internal mammary arteries. Given the conflicting results that have been published in literature over the last few years,<sup>2</sup> it seems safe to conclude that vasoactive competence of the AT<sub>2</sub> receptor is inferior to that of the AT<sub>1</sub> receptor.

Three important general matters considering UAE also need to be discussed here. First, in the present thesis we did not evaluate or discuss the methods we used for measuring UAE. Several methods have been described and they all have their (dis)advantages.<sup>3</sup> The golden standard, however, continues to be the procedure of collecting a 24 hour urine, which reduces the influence of circadian rhythm.<sup>4</sup> We have used several different collection methods in this thesis and we realize that this may have influenced the outcome.

The second issue that needs to be addressed is the current status of increased UAE. Without a doubt the finding of elevated UAE predicts the occurrence of future cardiovascular events. Therefore, elevated UAE seems to link renal to cardiovascular damage. Yet, it is still unclear whether UAE is a risk marker or a risk factor for cardiovascular disease. In diabetics with or without chronic renal disease reduction of UAE by blocking the RAS is accompanied by an improvement of renal prognosis.<sup>5-7</sup> A causal link between renal damage and UAE may be suspected and accordingly, elevated UAE is considered to be a risk factor for renal damage. In hypertensive patients and in the general population the pathophysiological role of elevated UAE as a cardiovascular prognostic tool is more controversial. In hypertensive patients UAE is often thought to be a reflection of generalized endothelial and vascular dysfunction.<sup>8</sup> In accordance with this theory, some authors found increased transcapillary escape rates of

albumin,<sup>9</sup> others found elevated levels of markers of inflammation (e.g. CRP) in microalbuminuric patients,<sup>10</sup> and some found elevated levels of markers of endothelial dysfunction in diabetic patients with elevated UAE.<sup>11</sup> To date, the question whether urinary albumin excretion simply is an epiphenomenon or actually causes cardiovascular disease has not been answered yet.

Third, as we demonstrated in Chapter 7, a large proportion of the UAE reducing potency of ACE inhibitors is the result of the intrinsic blood pressure-lowering effect of these agents. Specific postglomerular vasodilation and concomitant transglomerular pressure reduction, are thought to be responsible for their superior antialbuminuric properties. Yet, other non-blood pressure-related mechanisms such as reduction of Transforming Growth Factor  $\beta_1$  and Vascular Endothelial Growth Factor, may be involved as well in the renoprotective effects of ACE inhibitors and angiotensin receptor blockers (ARBs).<sup>12;13</sup> Whether UAE can be used as a marker of endothelial dysfunction remains a question, especially when patients are already using an ACE inhibitor or an ARB, as the specific renal effects of these agents may conceal changes in UAE due to improvement of endothelial function. In the present thesis no clues are found that circulating RAS parameters are involved in this process.

The relationship between elevated UAE and the activity of the RAS merits discussion as well. Even in patients with an activated RAS we did not find a direct association between activity of the systemic RAS and UAE. This leads us to believe that blockade of systemic angiotensin I breakdown into angiotensin II seems to be of minor importance in the beneficial cardiovascular action of ACE inhibitors that has been reported.<sup>14;15</sup> However, locally generated angiotensin II may be involved in the process that leads to extravasation of plasma albumin and consequent inflammation and atherosclerosis. In parallel to this theory, the RAS may still play a role in the renoprotective properties of these agents as well. In this context, it is important to gain knowledge of the association between circulating and local RAS activity. It is tempting to assume that circulating RAS activity reflects the activity of the local cascade, but assessing local renal and vascular RAS activity *in vivo* remains a technical challenge.

Importantly, measuring the parameters of the RAS in a venous blood sample is not as easy as it seems. Both physiological and biochemical factors may influence the levels measured, which renders them less useful as markers in a routine clinical setting. These two limitations may partly explain the lack of association between RAS activity and UAE. A third possibility involves the pathophysiological mechanism underlying the effect of ACE inhibitors: the favorable effects of these agents on the RAS may be overestimated, while we should be focusing on the kallikrein kinin system.<sup>16</sup>

### Future considerations

Measuring UAE is a routine test for nephrologists, and the most recent European Society of Cardiology hypertension guidelines recommend that this test should be performed in all hypertensive patients (and is essential in all diabetic patients).<sup>17</sup> However, many cardiologists still have to discover the value of the test in daily clinical practice. This simple and inexpensive test may be useful in the decision to start therapy, and even to monitor the effect of the prescribed pharmacological intervention. A second advantage of collecting urine is the possibility (or opportunity ?) to evaluate individual sodium excretion, and estimate sodium (and protein) intake (thus assessing dietary compliance), especially in chronic heart failure patients.

Many studies indicate that medications that reduce UAE may provide significant long term cardiovascular benefits for patients with hypertension, diabetes or chronic kidney disease.<sup>18-26</sup> Given the beneficial effects of ACE inhibitors and ARBs it will be interesting to see whether the novel RAS inhibitors, such as selective aldosterone receptor blockers and the latest oral renin inhibitors, will also provide end organ protection. Preliminary studies in rats and humans indicate that both eplerenone and aliskiren may protect the kidney,<sup>27,28</sup> and that eplerenone may have additional cardiovascular protective properties in selected patients.<sup>29</sup>

Obviously, prevention of (the progression of) end organ damage is an important issue. However, the PREVEND Intervention Trial study demonstrated that in mainly non-diabetic, normotensive, microalbuminuric subjects, fosinopril-induced UAE reduction was also associated with a trend in reducing cardiovascular events.<sup>15</sup> These results suggest that we should screen the general populations for elevated UAE and subsequently turn the subjects found positive into patients and actually treat them with an ACE inhibitor (or an ARB?). Even though pharmaco-economic analysis of the PREVEND study suggested that this strategy may be cost-effective,<sup>30</sup> other authors found paradoxical results.<sup>31</sup> In the present thesis we demonstrate that in normotensive, non-diabetic subjects UAE is determined by sodium excretion, and thus sodium intake. This suggest that modifying the patients diet should be the first sensible step to take, instead of prescribing medication. To reduce the burden on the health care system, future studies should address this issue, and selection criteria for screening patients that qualify for primary prevention should be developed. In secondary prevention, the importance of UAE reduction has been recognized for years.

In chronic heart failure patients the cause of UAE and the value of measuring UAE, need further exploration. In these patients and in diabetics, current guidelines already recommend starting an ACE inhibitor or an ARB,<sup>32;33</sup> so reduction of UAE in these patients may be a complimentary side effect. However, we do not know whether cardiovascular protection requires the same dosage as renoprotection.

Another issue that still needs to be resolved is the selection of patients that may benefit from combination therapy. Indeed, recent clinical trials suggest superior renoprotective and cardioprotective effects<sup>34;35</sup> of dual RAS blockade in selected populations, but no selection criteria for the individual patient are currently available. Clearly, further studies are needed to answer this question and to define optimal treatment protocols.

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