

Summary

The kidneys are responsible for regulating the body's fluid volume, mineral composition and acidity. In order to do so, the kidneys depend on an adequate cardiac output. When the cardiac output is reduced, the interplay between kidneys and endocrine tissue will provoke activation of the renin angiotensin system. This neurohormonal cascade forms a strong link between the heart and kidneys. For example, patients with end-stage renal disease are at increased risk of developing cardiovascular disease. Having a less severe renal dysfunction also carries a reduced cardiovascular prognostic value. In Chapter 2 we evaluate the prognostic value of preoperative renal function in over 400 patients undergoing coronary artery bypass grafting (CABG). This post-hoc analysis demonstrates that even a mild renal dysfunction will negatively affect (cardiovascular) prognosis of patients after CABG surgery.

When a chronic heart failure patient develops microalbuminuria, this is usually accompanied by an impaired prognosis as well. Several theories deliberate on the possible origin of microalbuminuria in these patients. One of these theories states that elevated urinary albumin excretion is a reflection of generalized endothelial dysfunction, while another theory suggests hyperfiltration as the underlying mechanism. Possibly, intact nephrons are forced to take over the filtration function of damaged nephrons, which leads to urinary albumin loss. In Chapter 3, a study with 96 severe chronic heart failure patients is described, in which we evaluate the prevalence of microalbuminuria. In 32% of these patients we found elevated urinary albumin concentrations. When this percentage is compared to the prevalence of microalbuminuria in the general population (represented by an age-matched group derived from the PREVEND study) it becomes clear that microalbuminuria is significantly more prevalent in chronic heart failure patients. Other authors demonstrated that antagonists of the renin angiotensin system, such as ACE inhibitors and angiotensin receptor blockers, can effectively reduce elevated urinary albumin excretion. This suggests a relationship between urinary albumin excretion and the renin angiotensin system. In our population, the activity of the circulating renin angiotensin system was increased in the microalbuminuric subjects, but the difference did not reach statistical significance.

When left ventricular function is impaired, which is the case in patients with severe chronic heart failure, the kidneys will respond with increased excretion of the peptide renin. The increased activity of renin will induce breakdown of angiotensin I into angiotensin II. This octapeptide will trigger aldosterone release. As a result, the kidneys will excrete less sodium and less water. The resulting volume overload will eventually induce typical clinical symptoms (e.g.

in chronic heart failure). This process can be delayed by blocking the detrimental effects of the renin angiotensin system. ACE inhibitors have repetitively demonstrated to inhibit the breakdown of angiotensin I into angiotensin II and, by doing so, to improve prognosis in chronic heart failure patients. However, in a considerable percentage of these patients elevated plasma angiotensin II levels can be found, despite the use of an ACE inhibitor (the so-called “ACE-escape”). In Chapter 4 the activation pattern of the renin angiotensin system in 99 severe chronic heart failure patients (New York Heart Association III and IV) is discussed. First, we determined the number of patients in whom angiotensin II levels remained elevated (>16 pmol/L) despite the use of a stable dose of an ACE inhibitor. In a second analysis we identified and evaluated the variables associated with elevated angiotensin II levels. In this study we demonstrated that 45% of our severe chronic heart failure patients have elevated angiotensin II levels despite treatment. Furthermore, the analysis demonstrated that the use of an aldosterone receptor antagonist was the only variable associated with elevated angiotensin II levels, which suggests the presence of a feedback mechanism within the renin angiotensin system. Renal function, dosage and duration of use of the ACE inhibitor seemed to have no predictive value for the occurrence of ACE-escape.

Activation of the renin angiotensin system induces higher angiotensin II and aldosterone levels in the human body. Previous investigators demonstrated that both of these hormones have a range of detrimental effects on the cardiovascular system. The effects of angiotensin II are mediated by stimulation of several receptors, of which the angiotensin II type 1 receptor (AT1R) and the angiotensin II type 2 receptor (AT2R) are the most important. The general opinion is that both these receptors mediate opposing effects. For example, stimulation of the AT1R will induce vasoconstriction, while stimulation of AT2R is thought to induce vasodilation. However, evidence for the latter is contradictory, and in humans also very limited. For this reason we performed the experiments that are reported in Chapter 5. In human internal mammary arteries which were harvested during coronary artery bypass surgery, we evaluated the effect of stimulation of the AT2R on the diameter of the arteries. The experiments demonstrated that both AT1R and AT2R can be found in these blood vessels. Stimulation of AT2R does not induce vasodilation in this experimental model.

Elevated urinary albumin excretion is associated with impaired prognosis. In analogy, lowering of urinary albumin excretion by using ACE inhibitors or angiotensin receptor blockers will improve cardiovascular prognosis. In Chapter 6 we discuss the combined approach: an angiotensin receptor blocker on-top-

of an ACE inhibitor. The theoretical considerations, the indications and the scientific evidence are presented.

The PREVEND intervention trial demonstrated that urinary albumin excretion can be reduced in non-cardiac patients as well. In addition, this study showed that this reduction is accompanied by an (almost significant) improvement of prognosis. In Chapter 7 we identify the variables that are associated with higher baseline levels of urinary albumin in patients from the PREVEND intervention trial. After multivariate regression analysis three variables are associated with a high baseline urinary albumin level: reduced renal function, elevated mean arterial blood pressure, and high sodium intake. This suggests that modification of diet may influence urinary albumin excretion. In addition, we demonstrate that the antialbuminuric effects of ACE inhibitors are partially independent of their blood pressure-lowering effect. Finally, we discuss the variables that determine the antialbuminuric effects of the ACE inhibitor. In this non-diabetic population baseline urinary albumin excretion seems to be the only independent determinant, meaning that the higher baseline the urinary albumin excretion, the more effective is the ACE inhibitor. This is reassuring, because it indicates that ACE inhibitors can be used independent of age, gender, or any other biological characteristic.