CHAPTER 1

Introduction and aim of the thesis
**INTRODUCTION**

Chronic kidney disease is a worldwide health problem and has a tremendous impact on both quality of life and mortality. Population based research suggests for example that 11% of the US adult population suffers from chronic kidney disease\(^1\), which results in poor outcome and high health care costs. Renal insufficiency, defined as a reduced glomerular filtration rate (GFR) or presence of albuminur...
Introduction

myocardial infarction\textsuperscript{21}, left ventricular dysfunction\textsuperscript{22}, and coronary artery disease with preserved left ventricular function\textsuperscript{23}. In these conditions, the ACEi is a protective therapy for respectively progressive kidney or heart function losses. ACEi are underutilized in chronic kidney disease patients with an acute myocardial infarction or an acute coronary syndrome\textsuperscript{24}. This might be due to physician concern regarding a further decrease of GFR. Therefore, much effort could be gained by optimization of ACEi prescription in these patients.

**Figure 2.** Role of intrarenal angiotensin II in the regulation of solute and water homeostasis in heart failure patients (adapted from Humes et al.\textsuperscript{26}).

---

**The Kidney in Heart Failure: Cardio-renal Interaction**

Under physiological circumstances, renal blood flow (RBF) and GFR are kept constant over a wide blood pressure range by autoregulation mainly located in the afferent and efferent vasculature of the glomeruli in the kidney. When cardiac output decreases, as in heart failure, systolic blood pressure will drop below this autoregulation range\textsuperscript{25}, under which circumstances GFR will follow arterial pressure causing hypoperfusion and hypofiltration and therefore ischaemia (figure 2). As a result, the RAAS is activated by secretion of renin, which leads to an increase in conversion of angiotensin I by the angiotensin converting enzyme (ACE) in angiotensin II causing systemic vasoconstriction and sodium retention in the kidney, thereby leading to an increase in effective circulating volume. In heart failure, this response results in a negative spiral not only consisting of RAAS activation, but also sympathetic nervous system activation, endothelial dysfunction, inflammation, and an impaired reactive oxygen/nitric oxide balance (figure 1). Upon the interaction of these systems, an even faster decline in cardiac and renal function occurs.

In patients that suffer a cardiovascular event, renal function data from before the event are often not available. In light of the predictive value of renal dysfunction on cardiovascular outcome, it is indispensable to have an animal model mimicking the clinical situation. Van Dokkum et al. described that the combination of mild renal function loss and mild cardiac damage resulted in progressive renal function loss, while no change in kidney function was seen after the single organs were mildly damaged\textsuperscript{27}. This interaction model provides a tool to study cardiorenal interaction and the effects of pharmacotherapy in laboratory animals.

**The Heart in Renal Failure: Renocardiac Interaction**

In end stage renal failure, the incidence of left ventricular hypertrophy and coronary artery disease...
Chapter 1

are 75 and 40%, respectively\(^\text{14}\). Within 2 years after start of dialysis, about half of these patients will experience a myocardial infarction (MI) with high mortality and poor long-term survival\(^\text{28}\). Even patients with impaired renal function, although not needing dialysis yet, have an increased risk to develop a cardiovascular event in the general population\(^\text{29}\) and in the already cardiac compromised population\(^\text{30}\). In uremic patients, the locally altered renal hemodynamics activate the RAAS causing sodium retention and an increase in efferent vascular resistance. This in turn results in an increase in systolic blood pressure, increase in extra cellular fluid volume and consequently volume overload leading to left ventricular hypertrophy.

Several structural and functional alterations of the heart and vasculature were observed in uremic patients and experimental uremic animals contributing to the increased risk for cardiovascular disease\(^\text{31}\):

- Capillary/myocyte mismatch: in experimental renal failure, left ventricular hypertrophy is associated with an increase in cardiomyocyte diameter and volume\(^\text{32-35}\) and a decrease in capillary length density\(^\text{36-37}\), which leads to an increased risk of hypoxia to the cardiomyocytes.
- Decreased cardiac output: in 5/6 nephrectomized rats, a decreased cardiac output was measured in the isolated heart\(^\text{38}\).
- Upregulation of the endothelin system: this was measured in renal disease by an increased ET-1 protein expression in the heart of subtotal nephrectomized rats\(^\text{39}\) and in the heart of uremic patients\(^\text{40}\).
- Increased atherosclerosis: the incidence of atherosclerotic complications is abnormally high in patient with chronic renal failure\(^\text{41}\).
- Reduced ischemic tolerance of the heart after myocardial infarction in already uremic animals\(^\text{42}\).

This indicates a substantial clinical problem: uremic patients are more susceptible to suffer from a myocardial infarction, and moreover, when they experience a myocardial infarction, the infarcted area might be more extensive than in non uremic patients.

To study reno-cardiac interaction, the 5/6 renal ablation model is a well evaluated model: activation of the RAAS by a substantial loss in nephron number results in hypertension, proteinuria, left ventricular hypertrophy\(^\text{43}\), cardiac capillary/myocyte mismatch\(^\text{44}\), reduced ischemia tolerance\(^\text{42}\) and reduced cardiac output\(^\text{38}\).

**Therapeutic Perspectives**

Intervention in the RAAS does reduce the risk for renal disease progression in renal patients, and the cardiac disease progression in cardiac patients. This protection goes beyond the effect that such drugs have on blood pressure. Despite the fact that this class of drugs has had tremendous impact on renal and cardiac health, patients with these diseases still run a considerable risk to die from cardiac or renal disease. Interestingly, some patients show a nearly complete protection, whereas other do not respond at all. This so-called inter-individual response variation is considerable\(^\text{45}\). Different mechanisms for therapy resistance have been hypothesized and investigated in both clinical and experimental settings, such as: sodium status\(^\text{46}\), ACE gene polymorphism\(^\text{47}\), different levels of activation of the RAAS\(^\text{48}\), and the amount of renal damage prior to ACE inhibitor therapy\(^\text{49}\). Beside the RAAS, there are other peptide systems interfering with these disease processes, like the natriuretic peptide system, the vasopressin system, and the endothelin system (figure 3).
Introduction

The balance between the net effect of vasoconstrictors and vasodilators determine the amount of vasoconstriction, sympathetic outflow, proliferative effects, aldosterone secretion and sodium retention. Vasoconstrictors are angiotensin II en endothelin-1. The secretion of these compounds are inhibited by ACE inhibitors and ECE inhibitors respectively. Natriuretic peptides and bradykinin are important vasodilators and these are stimulated by vasopeptidase inhibitors. These system are described below because they have been defined as an additional target for improving and/or replacing ACEi therapy in renal and cardiovascular diseases, which could help to overcome the previously mentioned therapy resistance to ACEi.

Natriuretic peptide system

It is well established that the natriuretic peptide system is intimately involved in the control and regulation of blood pressure and plasma volume in the body. In humans, this peptide family consists of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). Natriuretic peptides are degraded by the metallopeptidase neutral endopeptidase enzyme (NEP). ANP is produced in the atria and its production is stimulated by endothelin, vasopressin and catecholamines. Atrial wall tension, which can occur as a result of intravascular volume expansion, can also stimulate ANP production\(^{50}\).

The hemodynamic actions of natriuretic peptides within the cardiovascular system occur at many levels and include reducing preload, sympathetic tone, and increasing venous capacity. Natriuretic peptides act on both the heart and the kidneys by vasodilatation, natriuresis, diuresis, decreased cell growth, inhibition of the sympathetic nervous system, and inhibition of the RAAS\(^{51}\). Beside ACE-inhibition, NEP-inhibition (although controversial) as well has been shown to be protective in progressive function loss of either the kidney or the heart\(^{52-55}\). The combination of ACE and NEP inhibition, known as vasopeptidase inhibition, is claimed to be more effective in this regard\(^{56-60}\).
**Endothelin system**

The endothelin system is one of the most effective vasoconstrictive systems. The release of endothelin-1 (ET-1) is regulated by vasoconstrictor-, profibrotic-, inflammatory and proliferative agents. Vasodilating agents inhibit the production of ET-1, which levels are elevated in patients with heart failure and predict adverse clinical outcomes including mortality. Beside the relation to heart failure, ET-1 induces renal vasoconstriction, stimulate mesangial cell proliferation and matrix accumulation leading to glomerulosclerosis and interstitial fibrosis. To prevent these negative effects of ET-1 on the renal and cardiovascular system, reducing the formation of ET-1 by inhibition of the endothelin converting enzyme (ECE) is an option. Recently, inhibitors of the previously mentioned NEP and ECE have been developed. Combined inhibition of NEP and ECE results in increased activity of natriuretic peptides and reduced generation of endothelins resulting in vasodilation and blood pressure reduction. In experimental heart failure, ECE/NEPi already showed to be beneficial. The renal effects of combined NEP/ECE inhibition in experimental nephrosis are not known yet.

**Vasopressin system**

Vasopressin plays an essential role in regulating water balance and cardiovascular homeostasis. It is secreted from the posterior pituitary when the osmolarity of the plasma increases. Its renal effects are mediated through the V_1a_-receptor, localized in mesangial cells, efferent arteriole, vasa recta, and medullary interstitial cells, which induces an increase in glomerular filtration rate, and the V_2_-receptor, localized in the collecting ducts, which prevents water and sodium loss. In rats, vasopressin has been shown to contribute to hypertension, single nephron hyperfiltration, urinary protein excretion, and the progression of renal failure. Vasopressin receptor antagonists prevent development of proteinuria and hypertension in experimental renal failure. Beneficial effects of a V_1a_-receptor antagonist on cardiac function after experimental myocardial infarction were observed as well. The vasopressin system could therefore be a therapeutic target to interfere in the process of renal function impairment when renal damage is already established.

**Other specific strategies**

An alternative way to optimize the reno protective response of ACEi therapy, is specific delivery of an ACEi to the kidneys. Especially in patients with renal disease, although with no prominent blood pressure elevation, the maximal tolerated dose could be limited by the antihypertensive response. Renal delivery of ACEi could lead to optimal inhibition of renal ACE, without extra-renal side effects (like dry cough, angio-oedema), which can lead to discontinuation of the treatment. Kok et al. were able to target captopril specifically to the brush border of the renal tubules, where intrarenal ACE is located. Long-term effects on proteinuria are not known yet. Thus far, most pharmacological strategies in renal and cardiovascular disease have shown to be effective on both the heart and the kidneys. It would be of special interest to selectively improve kidney performance in cardiorenal interaction to observe the effect on the cardiac function. Drug targeting could be a good method to achieve this goal.
AIM OF THE THESIS

The vicious circle of the cardiorenal interaction results in an enormous clinical problem: patients with renal dysfunction are more susceptible to suffer a myocardial infarction. Moreover, when they experience a myocardial infarction, the infarcted area might be more extensive than in patients with normal renal function. Furthermore, renal damage will increase even more after myocardial infarction and vice versa. The aim of this thesis is therefore to get more insight in the mechanism and the pharmacological approach to interfere in the negative spiral of the cardiorenal interaction, especially with regard to the renin angiotensin aldosterone system and its related peptide systems.

In the first part of the thesis, we will explore the cardiorenal interaction to gain more insight in the mechanism and the responsiveness of this mechanism to RAAS intervention. In chapter 2, we investigate the responsiveness of a cardiorenal interaction model to RAAS intervention in order to prevent further renal damage. In chapter 3 we explore the effectiveness of ACEi on specific features of the cardiorenal interaction in an animal model with obvious renal and cardiac functional impairment caused by 5/6 nephrectomy and a myocardial infarction. To further explore the mechanism behind the cardiorenal interaction, we describe in chapter 4 if cardiac damage caused by renal failure is related to accelerated cellular aging. To this end, we measured telomere length in the heart of rats with combined and isolated cardiac and renal damage.

The second part of the thesis focuses on alternative therapeutic approaches to ACEi in rat models for renal and cardiac damage. We will investigate whether these therapeutic approaches will be effective in the prevention of renal and cardiovascular damage. In chapter 2 we evaluate if a combined ACE/NEP inhibitor, also referred to as vasopeptidase inhibitor, is more effective than an ACE inhibitor in the prevention of further renal damage in a cardiorenal interaction model. Whether combined ECE/NEP inhibition is not only effective on cardiac function, but might be effective on renal function as well, is described chapter 5. In chapter 6, a comparison will be made between a vasopressin 1a antagonist and an ACEi in early and late intervention in a renal ablation model. We describe the inter-individual variation in therapy response to an ACEi in the rat after 5/6 nephrectomy in chapter 7, to characterize possible targets to optimize pharmacotherapy. Chapter 8 focuses on selective renal delivery of ACEi in a rat model for renal failure.
REFERENCES


15. Brosius FC, III, Hostetter TH, Kelepouris E, Mitsnefes MM, Moe SM, Moore MA, Pennathur S, Smith GL, Wilson PW: Detection of Chronic Kidney Disease in Patients With or at Increased Risk of Cardiovascular Disease. A Science Advisory From the American Heart Association Kidney and Cardiovascular Disease Council; the Councils on High Blood Pressure Research, Cardiovascular Disease in the Young, and Epidemiology and Prevention; and the Quality of Care and Outcomes Research Interdisciplinary Working Group Developed in Collaboration With the National Kidney Foundation. Circulation 2006
72. Emoto N, Raharjo SB, Isaka D, Masuda S, Adiarto S, Jeng AY, Yokoyama M: Dual ECE/NEP inhibition on cardiac and neurohumoral function during the transition from hypertrophy to heart failure in rats. Hypertension 45:1145-1152, 2005