Chapter 1

Introduction and Aim of the Thesis

INTRODUCTION

Both left ventricular dysfunction, and renal dysfunction are world wide public health problems. In the western countries there is a rising incidence and prevalence of both conditions, with poor outcomes and high cost. These two conditions do often co-exist and the concomitant presence of both conditions accumulates risk for morbidity and mortality. In severe chronic heart failure (CHF), impaired renal function is often present, and is even a stronger risk marker than functional cardiac parameters, such as left ventricular ejection fraction or NYHA class.[1] On the other hand, left ventricular dysfunction is likely to develop in patients with chronic renal dysfunction (CRD) and accumulates with worsening renal function.[2] One of the first signs of left ventricular dysfunction in patients with CRD is left ventricular hypertrophy (LVH). Several studies have demonstrated an association between renal dysfunction and LVH and the prevalence of LVH increases with worsening of renal function.[3] Finally, several prevalence and longitudinal studies have shown that the well known age associated decline in renal function is more pronounced in patients with co-existing cardiovascular risk factors and pre-existing atherosclerotic vascular disease, suggesting that this decline is not a consistent phenomenon and reflect cardiovascular co-morbidity rather than normal aging.[4;5]

The cardiorenal axis

The association between cardiac and renal function described above, reflects more than a mere association, and in fact implies a causal interaction, which has gained a lot of interest over the last decades. Research has shown that both cardiac dysfunction and renal dysfunction affect each other through similar pathways.[6] This cardiorenal "cross-talk" is often referred to as the cardiorenal axis. Accordingly, hemodynamic alterations, renin-angiotensin aldosterone system (RAS) activation, sympathetic nervous system (SNS) activation, endothelial dysfunction, and inflammation are the main pathways involved and acting synergistically in the cardiorenal axis.

The systemic hemodynamic status has a central role. Changes, initially caused by either cardiac or renal impairment can initiate a cascade of mechanisms, which ultimately can lead to secondary end organ damage e.g. CHF or CRD.

In CHF inadequate cardiac output leads to arterial underfilling, which is sensed by various receptors. In response, vascular and neurohormonal mechanisms are activated in an attempt to provide compensatory mechanisms for the impaired cardiac output. However, these compensatory mechanisms contribute to the reduction in renal blood flow, renal sodium retention and consequently pulmonary congestion. In this process the SNS and RAS play a key role. As the condition progresses endothelial function becomes more impaired, associated with further reduction in renal perfusion.[7;8] Furthermore, chronic inflammation contributes to (renal) vascular, but also to cardiac dysfunction.[9] All of these aspects are involved in the deterioration of renal function in CHF. However the extent of their involvement, and their pathophysiological interrelationships, remain unclear. Conversely, in CRD the RAS and SNS also play a key role. The adaptation to loss of renal function involves local changes in renal hemodynamics that activate the RAS. As a result of sodium

retention and increased vascular resistance the blood pressure is increased, which leads to both increased volume and pressure overload. In CRD anemia, due to erythropoietine deficiency, can result in a volume overload. Both anemia and high blood pressure increase the cardiac workload, leading to LVH or left ventricular dilatation, which are precursors of CHF.[10;11] Furthermore, loss of renal function is associated with the presence of endothelial dysfunction, higher levels of inflammatory markers and changing lipoprotein structure, all precursors of atherosclerosis.

The susceptibility to develop LVH might also be influenced by genetic factors. Several polymorphisms, especially of the RAS, have been related to the development of LVH.[12;13] RAS-polymorphisms have been shown to modulate RAS -activity or –responsiveness in several experimental and human settings.[14;15] However, it has been argued that the biological effects of a single polymorphism are not sufficient to cause LVH, but can make a difference in the presence of other pathophysiological risk factors for LVH.[16] Renal dysfunction is such a risk factor, but whether renal dysfunction influences the impact of genetic polymorphisms and LVH is unknown.

Detection of renal dysfunction

Early recognition of renal dysfunction is important. Renal damage is characterised by reduced glomerular filtration rate (GFR) and an increase in urinary albumin excretion (UAE).

The GFR refers to the ability of the kidney to clear the blood plasma of certain substances and can be measured using exogenous tracers, like inulin or iothalamate. However these measurements are expensive and time consuming and not routinely available in most cases. Alternatives are to measure 24h creatinine clearance or to estimate GFR by using several formulas.[17;18] The formulas are easy to obtain and are frequently used as marker for renal function in large-scale CHF trials.[1;19] However, these formulas are prone to bias, and have never been validated in CHF patients.

Increased UAE is thought to precede manifest renal dysfunction.[20;21] The pathogenic mechanisms leading to the development of increased urinary albumin levels are still not completely known. Blood pressure load and increased systemic vascular permeability, possibly due to early endothelial damage, seem to play a major role. Atherogenic processes, inflammation, RAS activity, increased oxidative stress and SNS activation are suggested to damage the endothelial layer and enhance the (renal) vascular permeability. Elevated UAE, especially microalbuminuria (30-300mg), is an important risk marker for cardiovascular and renal disorders in various conditions, such as diabetes and hypertension[22;23], but also in the general population.[24] In CHF increased levels of UAE are frequently observed.[25] Most of the mechanisms, which damage the endothelium, are activated in CHF, but their precise participation and or interactions remains to be elucidated.

This thesis

The current thesis focuses on several aspects of the cardiorenal axis. The starting-point is provided by the concomitant presence of left ventricular dysfunction and renal dysfunction. We review the clinical importance of renal failure, and evaluate to what extent several parameters of the cardiorenal axis contribute to the CRD in CHF. We will also study the

interrelationship between different parameters of renal function and genes in an environment of left ventricular dysfunction. Finally, we will study measurement methodologies and mutual pathogenic mechanisms that can link left ventricular dysfunction to renal dysfunction.

In **part I** prognostic and clinical importance of renal function impairment in CHF will be discussed. In moderate to severe CHF, as discussed earlier, estimated glomerular filtration rate (eGFR) is an important predictor of cardiovascular death. Whether this holds true for mild CHF as well remains to be elucidated. Therefore, in **chapter 2** we will evaluate the predictive value of eGFR for cardiovascular mortality in patients with early mild CHF.

The observed relation between impaired eGFR and cardiovascular mortality might be explained by renal dysfunction being a marker of generalised atherosclerosis. On the other hand, this relation might also be explained by an impaired renal perfusion when left ventricular dysfunction is present. This suggests that the predictive value of eGFR for cardiovascular mortality might be different between ischemic (atherosclerosis present) and non-ischemic (atherosclerosis not present) heart failure patients. Therefore, in **chapter 3** and **4,** the prognostic value of eGFR is compared between patients with ischemic and non-ischemic CHF. First, we will address this issue in mild CHF patients. Second, we will address this in severe CHF patients, and moreover, we evaluated the relation of neurohormones and renal function in both populations. In **chapter 5** the influence of renal (dys)function on the pharmacokinetics of a selective Na^+/H^+-exchange inhibitor in patients with CHF will be evaluated.

In severe CRD LVH is frequently present, as mentioned earlier. Whether mild renal dysfunction is related to LVH is unknown. Therefore, in **chapter 6** the presence of mild renal dysfunction will be related to electrocardiographically determined LVH.This study will be performed in the subjects participating in the Prevention of REnal and Vascular ENd-stage Disease (PREVEND) study. The PREVEND study is designed to prospectively investigate the natural course of albuminuria and its relation to renal and cardiovascular disease in a large cohort drawn from the general population.

Another factor related to the susceptibility to develop LVH is genetic predisposition, for instance by genetic variability in the RAS. In **chapter 7** we investigated whether renal function modulates the relation of RAS-polymorphisms with LVH.

In **part II,** methodological issues regarding assessment of renal dysfunction in patients with CHF will be addressed and pathways within the cardiorenal axis will be explored.

Most studies use creatinine based formulas to estimate renal function, but these formulas have never been validated in CHF. Therefore, in **chapter 8** several frequently used creatinine-based formulas are validated by comparing them to the true GFR in patients with CHF. In **chapter 9** the relationships between renal blood flow, GFR, parameters of endothelial function, systemic RAS and inflammation are determined in patients with CHF. Furthermore, we will focus on the amount of UAE in these patients and the course of UAE in relation to renal function.

Reference List

1. Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, Hampton JR, van Veldhuisen DJ. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. *Circulation*. 2000;102:203-210.

2. Cheung AK, Sarnak MJ, Yan G, Berkoben M, Heyka R, Kaufman A, Lewis J, Rocco M, Toto R, Windus D, Ornt D, Levey AS. Cardiac diseases in maintenance hemodialysis patients: results of the HEMO Study. *Kidney Int*. 2004;65:2380-2389.

3. Levin A, Singer J, Thompson CR, Ross H, Lewis M. Prevalent left ventricular hypertrophy in the predialysis population: identifying opportunities for intervention. *Am J Kidney Dis*. 1996;27:347-354.

4. Krop JS, Coresh J, Chambless LE, Shahar E, Watson RL, Szklo M, Brancati FL. A community-based study of explanatory factors for the excess risk for early renal function decline in blacks vs whites with diabetes: the Atherosclerosis Risk in Communities study. *Arch Intern Med*. 1999;159:1777-1783.

5. Manttari M, Tiula E, Alikoski T, Manninen V. Effects of hypertension and dyslipidemia on the decline in renal function. *Hypertension*. 1995;26:670-675.

6. Bongartz LG, Cramer MJ, Doevendans PA, Joles JA, Braam B. The severe cardiorenal syndrome: 'Guyton revisited'. *Eur Heart J*. 2005;26:11-17.

7. Abassi ZA, Gurbanov K, Mulroney SE, Potlog C, Opgenorth TJ, Hoffman A, Haramati A, Winaver J. Impaired nitric oxide-mediated renal vasodilation in rats with experimental heart failure: role of angiotensin II. *Circulation*. 1997;96:3655-3664.

8. Elkayam U, Cohen G, Gogia H, Mehra A, Johnson JV, Chandraratna PA. Renal vasodilatory effect of endothelial stimulation in patients with chronic congestive heart failure. *J Am Coll Cardiol*. 1996;28:176-182.

9. Fichtlscherer S, Rosenberger G, Walter DH, Breuer S, Dimmeler S, Zeiher AM. Elevated C-reactive protein levels and impaired endothelial vasoreactivity in patients with coronary artery disease. *Circulation*. 2000;102:1000-1006.

10. Sarnak MJ. Cardiovascular complications in chronic kidney disease. *Am J Kidney Dis*. 2003;41:11-17.

11. Pokharel S, Sharma UC, Pinto YM. Left ventricular hypertrophy: virtuous intentions, malign consequences. *Int J Biochem Cell Biol*. 2003;35:802-806.

12. Ohishi M, Rakugi H, Ogihara T. Association between a deletion polymorphism of the angiotensin-converting-enzyme gene and left ventricular hypertrophy. *N Engl J Med*. 1994;331:1097-1098.

13. Kuznetsova T, Staessen JA, Wang JG, Gasowski J, Nikitin Y, Ryabikov A, Fagard R. Antihypertensive treatment modulates the association between the D/I ACE gene polymorphism and left ventricular hypertrophy: a meta-analysis. *J Hum Hypertens*. 2000;14:447-454.

14. Buikema H, Pinto YM, Rooks G, Grandjean JG, Schunkert H, van Gilst WH. The deletion polymorphism of the angiotensin-converting enzyme gene is related to phenotypic differences in human arteries. *Eur Heart J*. 1996;17:787-794.

15. van Geel PP, Pinto YM, Voors AA, Buikema H, Oosterga M, Crijns HJ, van Gilst WH. Angiotensin II type 1 receptor A1166C gene polymorphism is associated with an increased response to angiotensin II in human arteries. *Hypertension*. 2000;35:717-721.

16. Schunkert H. Controversial association of left ventricular hypertrophy and the ACE I/D polymorphism-is the mist clearing up? *Nephrol Dial Transplant*. 1998;13:1109-1112.

17. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31-41.

18. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130:461-470.

19. Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, White HD, Nordlander R, Maggioni A, Dickstein K, Zelenkofske S, Leimberger JD, Califf RM, Pfeffer MA. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med*. 2004;351:1285-1295.

20. Mogensen CE. Prediction of clinical diabetic nephropathy in IDDM patients. Alternatives to microalbuminuria? *Diabetes*. 1990;39:761-767.

21. Pinto-Sietsma SJ, Janssen WM, Hillege HL, Navis G, de Zeeuw D, de Jong PE. Urinary albumin excretion is associated with renal functional abnormalities in a nondiabetic population. *J Am Soc Nephrol*. 2000;11:1882-1888.

22. Mattock MB, Morrish NJ, Viberti G, Keen H, Fitzgerald AP, Jackson G. Prospective study of microalbuminuria as predictor of mortality in NIDDM. *Diabetes*. 1992;41:736-741.

23. Ljungman S, Wikstrand J, Hartford M, Berglund G. Urinary albumin excretion—a predictor of risk of cardiovascular disease. A prospective 10-year follow-up of middle-aged nondiabetic normal and hypertensive men. *Am J Hypertens*. 1996;9:770-778.

24. Hillege HL, Janssen WM, Bak AA, Diercks GF, Grobbee DE, Crijns HJ, van Gilst WH, de Zeeuw D, de Jong PE. Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. *J Intern Med*. 2001;249:519-526.

25. Eiskjaer H, Bagger JP, Mogensen CE, Schmitz A, Pedersen EB. Enhanced urinary excretion of albumin in congestive heart failure: effect of ACE-inhibition. *Scand J Clin Lab Invest*. 1992;52:193-199.

Part I

Prognostic and Clinical Importance of Renal Dysfunction and Left Ventricular Dysfunction