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New roles for renin in heart failure and cardio-renal interaction

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NEW ROLES FOR RENIN IN HEART FAILURE AND CARDIO-RENAL INTERACTION

Nicolas F. Schroten

New roles for renin in heart failure and cardio-renal interaction

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INTRODUCTION

EPIDEMIOLOGY OF HEART FAILURE AND KIDNEY DISEASE

Heart failure and kidney disease have a major impact on life expectancy and on our health care system. The prevalence of heart failure is estimated to be 1-2% in the general population and around 7-8% in subjects > 75 years. This number is, however, increasing due to improved therapeutic options to treat myocardial infarction and increasing age of the population at large. (1,2)

In parallel to heart failure, the prevalence of chronic kidney disease (CKD) is also increasing. In the Netherlands the prevalence of CKD is estimated between 5-7%, although the prevalence strongly increases with age. In subjects aged 75-79 years the prevalence of CKD was more than 25% in subjects without diabetes and even more than 50% in diabetics. (3) With an aging population and increasing prevalence of diabetes the prevalence of CKD will only rise further.

There is a close interaction between heart failure and kidney disease. Heart failure is often complicated by kidney disease and, vice versa, kidney disease is associated with an increased risk for cardiac disease. (4) This strong reciprocal relation has long been recognized and the term the cardio-renal syndrome has been applied to address this interdependency of the kidney and the heart. To better understand and categorize the relation(s) between heart and kidney disease a classification into 5 types of cardio-renal syndrome has been proposed, (5) subdividing cardio-renal syndrome in acute vs chronic and renal disease causing cardiac dysfunction vs cardiac disease causing renal dysfunction. The last group comprises patients with a systemic disease leading to both kidney and cardiac dysfunction. The mechanisms and sequence of events that lead to dysfunction of both organs is often unclear and it may be difficult to classify a patient, because the relation is often bidirectional and may vary within one patient over the course of the disease. Furthermore this classification is not useful to guide therapy, since it does not take into account the underlying pathophysiological mechanisms. Therefore a better classification based on underlying pathology is much needed.

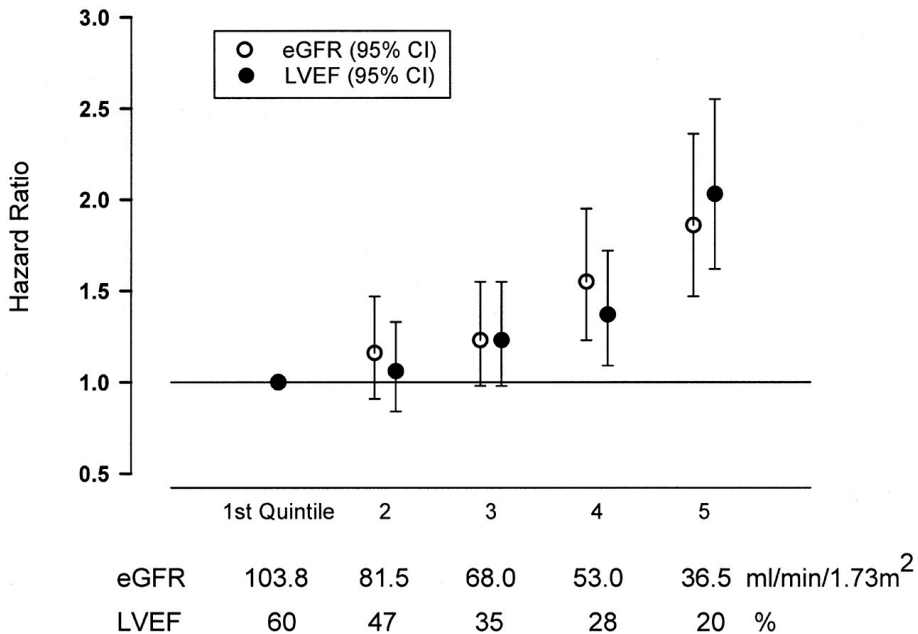
Patients hospitalized for heart failure have a poorer prognosis than most types of cancer, (6) likewise patients on dialysis have an average survival of 9 years for patients between 40-44 years and only 4.5 years for patients between 60-64 years.

(7) But irrespective of the type of cardiorenal syndrome, concomitant presence of both heart failure and kidney disease has a large impact on prognosis; kidney disease accompanying heart failure further worsens prognosis, and heart failure accompanying kidney disease also impairs survival. What is striking is that renal function is a just as strong a predictor for hospitalisation and mortality in heart failure patients as cardiac parameters like left ventricular ejection fraction. (8) (figure 1)

PATHOPHYSIOLOGY OF THE CARDIORENAL SYNDROME

The pathophysiology of the cardio-renal syndrome is complex and not fully understood. Several mechanisms have been proposed to explain the correlation between heart failure and renal dysfunction. (9,10) In brief, they can be categorized into hemodynamic factors, neurohormonal factors, inflammation, oxidative stress and therapy.

FIGURE 1. MULTIPLE ADJUSTED HAZARD RATIOS (WITH THEIR 95% CI) FOR RISK OF CARDIOVASCULAR DEATH OR UNPLANNED ADMISSION TO HOSPITAL FOR THE MANAGEMENT OF WORSENING CHF ACROSS DECREASING EXACT QUINTILES (MEDIAN VALUES PRESENTED) OF BOTH EGFR AND LVEF. (HILLEGE ET AL. CIRCULATION. 2006; 113: 671-678)



HEMODYNAMIC FACTORS

Heart failure and kidney disease share several common risk factors. The most studied is hypertension, which is a well-known risk factor for ischemic heart disease, (11) heart failure with preserved ejection fraction (12) and kidney disease. (3) Long term hypertension can therefore lead to both heart failure and kidney disease, although which will occur first is variable. Furthermore heart failure is characterized by both decreased cardiac output and congestion. Traditionally, it was thought that decreased cardiac output would be the main determinant of decreased renal function in heart failure patients, but recent studies show that increased central venous pressure and congestion may be even more important. (13, 14) Atherosclerosis is another common pathway for both renal and cardiac disease and there is increasing evidence that decreased renal perfusion, e.g. due to renal artery atherosclerosis, is an often undiagnosed cause of renal dysfunction in heart failure patients. (15) In healthy individuals renal function can be maintained at a stable level despite moderate changes in blood pressure and renal blood flow, due to autoregulation of intraglomerular pressure. In heart failure, however, renal blood flow appears vital for maintaining GFR. (Chapter 5 and 6)

NEUROHORMONAL

Another well studied mechanism for both cardiac and renal disease is activation of the Renin-Angiotensin-Aldosterone-System (RAAS). RAAS blockers have become the cornerstone for treatment for both cardiac and renal disease. However, in the last decade, it has also become clear that the RAAS is more complex than previously thought (Chapter 2) and that RAAS inhibition is not always beneficial. Specifically, trials evaluating dual or triple RAAS blockade have produced troubling data, and nowadays dual or triple blockade is no longer recommended in heart and kidney disease because of little or absent clinical benefit, with increased (serious) side effects. The main side effects reported were hyperkalemia, hypotension and non-fatal stroke, probably relate to excessive reduction of blood pressure and tissue perfusion, furthermore an increased risk for hyperkalemia was observed (17, 18, 35).

It remains unclear if (inappropriate) RAAS activation in healthy individuals is a common risk factor for long-term cardio-renal disease. We demonstrated an association between high renin levels with incident cardiovascular disease, (chapter 3) but not with renal function decline (chapter 4). Other studies have also found conflicting results. (19-21)

Sympathetic nerve activation is yet another important factor in both cardiac and renal disease. This is supported by the observation that beta-blockers are

protective in heart failure and ischemic heart disease, but they also appear to prevent renal function decline. (22) Amongst others sympathetic nerve activity affects renin release, (23) but it has various other effects that are beyond the scope of this thesis. New techniques interfering in sympathetic nerve activation have recently been developed and are currently tested. (24) Hopefully they will shed more light on the exact role of the sympathetic nerve system in the cardio-renal axis.

INFLAMMATION, OXIDATIVE STRESS AND METABOLIC FACTORS

There appears to be an inflammatory status in both heart failure and kidney disease, since many inflammatory markers are elevated in both conditions, (25-27) and their levels are associated with poor prognosis. Furthermore there appears to be a state of oxidative stress in heart failure (28) and kidney disease patients, (29) which may be another explanation why injury or failure of one organ may lead to injury or failure in the other organ. Also metabolic factors may link renal and cardiac disease. For example, patients with end-stage renal disease show accelerated vascular calcification driven by high calcium and phosphorus levels. (30) The main hormones regulating calcium are parathyroid hormone and Vitamin D, but vitamin D may also link cardiac and renal diseases via another pathway. Vitamin D is activated in the kidney and observational studies have shown that low vitamin D levels are associated with increased incidence of cardiovascular disease. (31) One of the potential mechanisms for this association may be the inhibition of renin transcription by active vitamin D. (Chapter 7) Few drug trials, however, have been performed that interfere in the oxidative stress, inflammatory and metabolic pathways, therefore it is unknown if modulation of these pathways will improve prognosis. One exception is diabetes, where it has clearly been demonstrated that early good glucose regulation can prevent both kidney disease and cardiac events. (32)

THERAPY

The impact of medical treatment is often underrepresented in the discussion about cardio-renal pathways. Many drugs used to treat cardiac disease affect kidney function. Diuretic treatment is clearly associated with worsening renal function, (33) but also most RAAS blockers can cause a (temporary) decrease in GFR. Interestingly a moderate decrease in GFR when initiating RAAS blocking therapy is not always harmful. (34) Furthermore contrast used during cardiac catheterisations can cause contrast-induced nephropathy.

AIMS OF THIS THESIS

This thesis aimed to further clarify the role of the RAAS and specifically renin in the pathophysiology of cardio-renal syndrome. Chapter 2 describes what is known so far on the role of renin in heart failure and cardio-renal interaction and provides the rationale for the studies performed in this thesis. Chapter 3 and 4 explore the role of renin in the early development of cardiac and renal disease, by investigating the relation of high renin levels in healthy individuals with cardiac events and renal function decline. Chapter 5 studies the risk factors for renal function decline in chronic heart failure patients and describes renal hemodynamics in these patients. In Chapter 6 and 7 studies investigating new therapies in heart failure targeting the RAAS system are presented. Chapter 6 describes the effect of a direct renin inhibitor on renal blood flow in heart failure patients with moderate renal dysfunction and chapter 7 investigates if vitamin D can suppress RAAS activation in chronic heart failure patients.

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