Chapter 1

Introduction and Aim of the Thesis.
Chapter 1

Left ventricular dysfunction

This thesis deals with left ventricular (LV) dysfunction. A problematic aspect of this pathology is its progressive character, eventually leading to chronic heart failure (CHF). The end stage - chronic heart failure - is a disease which is characterized by a grave prognosis, with a 5-year survival of ±25%\(^1\). Furthermore, heart failure is an immobilizing disease, which is characterized by impaired exercise capacity and edema in lungs and limbs, and is associated with numerous hospitalizations. Currently, as much as 1-2% of the general population in developed countries suffers from heart failure, and its prevalence is increasing\(^2\).

Figure 1 illustrates the development and progression of LV dysfunction in time, starting with an index event. In the majority of cases this event is myocardial infarction\(^3,4\). Myocardial infarction causes a loss of contractile LV tissue, which leads to structural remodeling of the infarct area (scar formation), but also of the remaining viable tissue. The latter initiates a downward spiral of further deterioration of cardiac pump function and remodeling (figure 1). Eventually this leads to the clinical syndrome of chronic heart failure.

LV remodeling involves cardiomyocyte hypertrophy, which results in a relative reduction of capillary density and increased oxygen diffusion distance, and a subsequent deterioration of cardiomyocyte metabolism and function. A second key process in LV remodeling is proliferation of fibroblasts and fibrosis, which stiffens the ventricle and impairs cardiac contractility. Thirdly, the progression of LV dysfunction towards chronic heart failure after myocardial infarction is accompanied by increasing peripheral vascular resistance, which is a result of reduced production of endothelium-derived vasodilator substances\(^5,6\) and myogenic constriction of resistance arteries\(^7\). This may serve as a mechanism to compensate for reduced cardiac output to redistribute blood flow to the organs. However the increase in peripheral resistance may become excessive and actually trigger the progression of LV dysfunction\(^8,9\).

Excess activation of physiological compensatory regulation systems, in particular the renin-angiotensin-aldosterone system (RAAS), plays a central role in all these processes mediating the development of chronic heart failure. Hence, pharmacological intervention with the RAAS substantially improves prognosis of patients with LV dysfunction.

ACE inhibitor therapy

Intervention with the RAAS by inhibition of the angiotensin I converting enzyme (ACE) is first-line therapy to attenuate the progression of LV dysfunction. ACE inhibitors were initially designed as vasodilator drugs about 25 years ago to treat high-renin hypertensive patients, and to reduce fluid overload symptoms in patients with heart failure. The mechanism by which ACE inhibition attenuates the progression of left ventricular dysfunction was initially thought to be vasodilation, resulting in reduced cardiac workload, as ACE inhibition prevents the degradation of the vasodilating peptide bradykinin, and the formation of the vasoconstricting peptide angiotensin II. However, superiority of ACE inhibitors over directly acting vasodilator
drugs to reduce mortality and improve of cardiac function\textsuperscript{10,12} clearly pointed towards effects beyond vasodilation. By now, a vast amount of evidence has shown that angiotensin II directly triggers cardiomyocyte hypertrophy and cardiac fibrosis on the cellular level, and conversely that RAAS blockade effectively inhibits cardiac and vascular remodeling processes. ACE inhibitors provide protection against end-organ damage in several cardiovascular pathologies: renal failure, diabetic nephropathy, hypertension, LV dysfunction after myocardial infarction, and overt CHF. During the last two decades, numerous landmark trials have unambiguously shown that ACE inhibition improves cardiac function\textsuperscript{13}, prognosis\textsuperscript{14}, and quality of life\textsuperscript{15} in patients with myocardial infarction and/or chronic heart failure.

\section*{Sodium restriction}

Although ACE-inhibition slows the gradual progression of myocardial dysfunction towards overt chronic heart failure (CHF), it does not prevent it. Hence, morbidity and mortality remain high, and further optimization of therapy is warranted. Apart from developing new strategies that intervene with remodeling via different mechanisms, one should ask whether current treatment options are used optimally. In this respect, an important potential target could be intervention with the sodium balance. In numerous studies, dietary sodium restriction has been shown to increase the efficacy of ACE-I treatment. This potentiation is consistently found across different clinical experimental conditions, including proteinuric renal dysfunction, and essential hypertension\textsuperscript{16-18}. Conversely, sodium loading can completely annihilate these
therapeutic effects of ACE inhibition19-20. However, intervention with the sodium balance is currently not used as a deliberate strategy to optimize the therapy response to ACE inhibition in patients with LV dysfunction. Before discussing the potential mechanisms underlying interaction between sodium depletion and ACE inhibition, effects of a negative sodium balance per se during LV dysfunction will be addressed.

Sodium depletion during left ventricular dysfunction

There are several strategies to induce a negative sodium balance, of which dietary sodium restriction is the first obvious approach. However, long-term patient compliance with low sodium diets is not always achieved. In clinical practice, sodium depletion with diuretics at a moderate salt intake may be more feasible, since diuretic therapy is easier to maintain. Moreover, approximately 30% of post-MI patients are currently treated with diuretics to reduce fluid overload symptoms. Non-potassium sparing diuretics, notably the loop diuretic furosemide, are the most potent and most frequently used diuretics to reduce fluid overload. Hence in patients with post-MI LV dysfunction this class of diuretics could serve for sodium depletion to optimize ACE-I therapy too. However, based on their longer duration of action and absence of peak diuresis, thiazide diuretics would be the first choice of treatment to use for this therapeutic strategy. Finally, of the different potassium-sparing diuretics, solely aldosterone receptor antagonists are sufficiently potent to promote sustained significant sodium excretion21,22.

The direct cardiac effects of these interventions are described below. Dietary sodium restriction or non-potassium sparing diuretics attenuate LV hypertrophy due to hypertension, mainly by mechanical unloading of the heart23. Also in an experimental model for myocardial infarction in combination with hypertension development of LV hypertrophy was shown to be attenuated by treatment with a loop diuretic24. However, in a situation of normal or even decreased blood pressure, - as is generally the case after myocardial infarction - effects of sodium depletion per se on LV remodeling may be minimal. Indeed, Sharpe et al. reported no effects of long-term furosemide treatment on left ventricular function in patients with moderate LV dysfunction after myocardial infarction25. Furthermore neither chronic dietary sodium restriction, nor treatment with hydrochlorothiazide or furosemide showed to affect development of LV hypertrophy in rats with myocardial infarction26-30. It was shown that thiazides and loop diuretics cause venodilation at therapeutic concentrations, but it remains uncertain whether this could beneficially influence the progression of LV dysfunction31-34.

Contrary to furosemide, the more recently developed loop diuretic torasemide was shown to beneficially affect LV remodeling. It significantly reduced morbidity and mortality compared to furosemide in the TORIC study, a randomized open-label trial in 1377 patients with heart failure35. Furthermore, the drug was shown to reduce myocardial fibrosis, while furosemide had no effect36. Thus, torasemide may prove to be preferable over furosemide in patients with left ventricular dysfunction, but double-blind randomized trials will be required. The most probable mechanism underlying these beneficial effects of torasemide may be interference with aldosterone. Firstly, it was shown that torasemide directly inhibits aldosterone synthesis in aldosterone-
 producing cells\textsuperscript{37}. Furthermore torasemide inhibited binding of aldosterone to its receptor\textsuperscript{38}. Aldosterone receptor antagonists effectively attenuate (aldosterone-mediated) LV remodeling and endothelial dysfunction, and reduce morbidity and mortality in patients with post-MI LV dysfunction\textsuperscript{39} and severe heart failure\textsuperscript{40}. To distinguish between effects of sodium depletion and aldosterone interference, diuretics directly interfering with aldosterone were not studied in the present thesis.

**Optimization of ACE inhibition with sodium depletion?**

In numerous studies, dietary sodium restriction was shown to augment the response to ACE-I therapy for renal dysfunction and essential hypertension\textsuperscript{16-18}. Despite the substantial amount of clinical and experimental evidence, the mechanisms underlying this potentiation by sodium restriction are poorly understood. The following section provides an overview of potential factors involved.

![Simplified RAAS scheme showing potential balance of detrimental and beneficial effects of angiotensin peptides. Activating the RAAS with sodium restriction during ACE inhibition may increase Ang-(1-7), shifting the ratio between effects of Ang II and Ang-(1-7).](image)

Presumably, activation of the RAAS is required for effective ACE inhibitor therapy. During ACE inhibition salt restriction may cause a shift of production of Ang II towards Angiotensin-(1-7) (Ang-(1-7), see figure 2). Increased production of Ang-(1-7) under...
ACE inhibition has been proposed to underlie at least part of the therapeutic effects. In line with this, Ang-(1-7) appears to act as a physiological antagonist of angiotensin II, and actually attenuates the progression of heart failure in rats with myocardial infarction. The observation that reduction of salt intake in humans treated with an ACE-I further increases plasma Ang-(1-7) concentrations argues in favor of this mechanism.

Secondly, sodium restriction may alter the expression of the Angiotensin II type 1 and 2 (AT1 and AT2) receptors. AT2-receptor stimulation has antihypertrophic and antifibrotic effects, counteracting the detrimental effects of AT1 stimulation (figure 3). During high dietary salt intake, expression of AT2 receptors decreases, while AT1 expression increases. Conversely, dietary sodium restriction could lead to a more favorable AT2/AT1 receptor ratio, causing the remaining Ang II that may be produced despite ACE inhibition actually to exert beneficial effects.

**Figure 3.** A scheme of the RAAS, showing its most biologically relevant peptides and enzymes. Grey boxes indicate physiologically active angiotensin peptides. Numbers between brackets indicate the sequence of amino acids in the different angiotensin-derived peptides.
Limitations of sodium depletion

Sodium depletion using diuretics is not by definition harmless, and may have unwanted effects. Firstly, thiazide and loop diuretics not only cause sodium depletion, but also increase the excretion of potassium and magnesium. Hypokalemia by chronic treatment can trigger cardiac arrhythmias, and indeed high doses of diuretic therapy have been associated with increased mortality due to ventricular arrhythmias in patients with LV dysfunction59-60. These results should however be interpreted with some caution, as these findings were done in post hoc studies, and diuretic-use is associated with severity of symptoms and cardiac impairment. Severity of cardiac dysfunction may be associated with incidence of ventricular arrhythmias, due to remodeling51. Secondly, diuretic therapy or dietary sodium restriction could cause further activation of the RAAS, which potentially accelerates cardiac remodeling. Indeed furosemide treatment caused accelerated progression towards severe heart failure induced by rapid pacing in pigs. This progression was associated with markedly increased plasma aldosterone concentrations, indicating further RAAS activation52. Treatment with an ACE inhibitor or AT1 receptor antagonist would theoretically block this RAAS-inducing effect of sodium depletion. However, a study in patients with mild-to-moderate heart failure showed that reduced sodium intake caused an increase in plasma aldosterone concentrations, albeit almost all patients were treated with ACE inhibitors63. This could be related to a phenomenon called “aldosterone escape”: high aldosterone concentrations despite ACE-I therapy54. This phenomenon may be caused by angiotensin conversion through chymase. Furthermore, ACE inhibitors can cause K+ retention, which in turn directly triggers aldosterone production. Aldosterone itself can aggravate LV dysfunction failure by causing endothelial dysfunction, fibrosis, and LV hypertrophy55-58. Aldosterone receptor antagonists are in this respect of obvious therapeutic importance, as apart from inducing natriuresis, they attenuate the deleterious effects of aldosterone (escape), and moreover have potassium-retaining effects. However, aldosterone antagonist-induced hyperkalemia occurs frequently, and is a serious concern, as it is associated with an increased risk of cardiovascular events59. Combining low doses of thiazide diuretics with aldosterone receptor antagonist is an option worth further study, as this strategy could establish efficient natriuresis without a net effect on potassium balance60.

Long-term ACE inhibition and its withdrawal

LV dysfunction after myocardial infarction is a structural disease of the heart, and ACE inhibition is not curative. Therefore ACE inhibition therapy should in principle be lifelong. However, about 10% of all patients do not tolerate ACE inhibitors due to serious side effects61. As a consequence ACE inhibitor withdrawal often occurs in clinical practice. In addition, discontinuation may occur because of patient’s incompliance62. Nevertheless, little has been described in literature about the actual consequences of cessation of therapy. This issue deserves attention for several reasons. Firstly, withdrawal of several cardiovascular drugs, such as β-blockers63, nitrates64, and statins65 can cause pronounced rebound effects, requiring stepwise cessation of therapy.
Furthermore, in the Captopril And Thrombolysis Study (CATS), withdrawal of chronic ACE inhibition after the trial period caused a high incidence of ischemia-related events within one month. As the expression of renin, the rate-limiting step in the RAAS cascade, is drastically increased during ACE inhibition therapy, occurrence of a rebound effect is probable. However, there are also arguments against pronounced detrimental effects of withdrawal. Antihypertensive effects of ACE inhibitors are sustained long after withdrawal in experimental models. Furthermore, the beneficial effects of ACE inhibition on mortality rates decrease over time, and consequences of cessation of chronic therapy may thus be limited.

**Aim of the thesis**

Summarizing the above, RAAS activation plays a major role in the progression of left ventricular dysfunction towards chronic heart failure. ACE inhibition therapy improves cardiac function and reduces morbidity and mortality. Although ACE-inhibition slows the gradual progression of myocardial dysfunction towards overt chronic heart failure (CHF), it does not prevent it. Apart from developing new strategies that intervene with remodeling via different mechanisms, one should ask whether current treatment options are used optimally. Accordingly, several issues concerning long-term efficacy and optimization of ACE-I therapy in relation to sodium status need further study. Hence, the aim of this thesis is to investigate the following two hypotheses:

1. Sodium depletion can safely be added to ACE inhibition therapy for left ventricular dysfunction after myocardial infarction, and does improve treatment outcome (chapters 2-5).
2. ACE inhibitor therapy still effectively blocks the RAAS after long treatment periods, and discontinuation results in rebound disease progression (chapters 6 and 7).

**References**


