Chapter 8

General Discussion.
Chapter 8

Introduction

Excess activation of the RAAS plays a central role in the progression of left ventricular dysfunction towards chronic heart failure after myocardial infarction. This system becomes activated to maintain sufficient cardiac output, and improve the clinical status of the patient in an acute setting. However, chronic activation of the RAAS mediates progressive cardiac remodeling. During the last two decades, inhibiting the RAAS with ACE inhibitors unambiguously proved to improve cardiac function and prognosis after myocardial infarction. Accordingly, ACE inhibition is the cornerstone of therapy to prevent the progression of left ventricular dysfunction.

Despite its undisputed benefits, ACE-inhibition slows down, but does not prevent the gradual progression of myocardial dysfunction towards overt chronic heart failure (CHF). Furthermore, not all patients show an optimal therapy-response to ACE inhibition. Hence, morbidity and mortality remain high, and further optimization of therapy is warranted. One potential target could be intervention with the sodium balance. In numerous studies, dietary sodium restriction was shown to augment the response to ACE-I treatment across different clinical and experimental conditions, including proteinuric renal dysfunction, and essential hypertension\textsuperscript{1-6}. However, this was not investigated yet for treatment of LV dysfunction and heart failure, and this was therefore the topic of the first part of this thesis.

Optimization of ACE inhibition with a low sodium diet?

Despite the substantial amount of clinical and experimental evidence, the mechanisms underlying this potentiation of ACE-I therapy by sodium restriction are poorly understood. It has been suggested that activation of the RAAS is required for effective ACE inhibitor therapy\textsuperscript{7}, because during ACE inhibition RAAS activation with sodium depletion may cause a shift of production of Ang II towards Ang-(1-7). Increased production of Ang-(1-7) under ACE inhibition has been proposed to underlie at least part of the therapeutic effects.

In chapter 2 we showed increased left ventricular ACE inhibition and LV hypertrophy reduction with dietary sodium restriction added to ACE-I therapy. The hypothesis of increased RAAS activity and Ang-(1-7) levels could not be tested in that study. In chapter 3 however, we observed no further increase in plasma renin activity by dietary sodium restriction in addition to ACE inhibition after long-term treatment. Thus it is questionable whether sodium depletion during ACE inhibition in rats with myocardial infarction results in further activation of the RAAS on the long term, explaining the lack of improvement of cardiac function and mortality.

Notably, these studies investigated effects of sodium restriction on ACE inhibition after an extensively long follow-up period; also in treatment of renal diseases the effects of reducing sodium intake on efficacy of ACE inhibition are documented only for intermediate parameters, i.e. proteinuria, blood pressure, and tissue ACE activity. However, based on our results, effects of sodium restriction on ACE inhibition on hard endpoints (morbidity, mortality) during a follow-up in the order of months to years should be studied in all clinical conditions for which ACE-I treatment is used.
**Beneficial effects of diuretic treatment**

Contrary to dietary sodium restriction, diuretic treatment with hydrochlorothiazide improved early chronic survival during ACE inhibitor therapy (Chapter 3). As hydrochlorothiazide added to ACE inhibition caused a decrease in plasma renin activity compared to ACE inhibition alone after 8 months of treatment, the early chronic survival benefit of hydrochlorothiazide was not caused by further RAAS activation. Rather, the explanation for this observation may be either a potentiation of ACE inhibition, or a direct effect of hydrochlorothiazide. HCTZ-mediated venodilation resulting in reduced preload (as shown by reduced LVEDP) could account for such a direct effect. Alternatively, a pharmacokinetic explanation could underlie the interaction between sodium depletion and ACE inhibitors. Interestingly, we found an interaction between HCTZ and two different ACE inhibitors: in chapter 4 we describe that diuretic treatment caused accumulation of ACE inhibitors in either plasma or cardiac and renal tissue, depending on the lipophilicity of the ACE-I.

The idea for a kinetic interaction already arose from results in chapter 2, where it was shown that ACE-I therapy caused a more pronounced reduction in tissue ACE activity under sodium depleted conditions. This, while sodium restriction *per se* does not influence tissue ACE activity. This finding suggests that during sodium depletion tissue concentrations of ACE inhibitors can be increased, reflecting improved tissue drug penetration.

Presumably, a volume depletion effect may underlie the accumulation, either directly, or via decreased renal clearance of the drug. Combining diuretic treatment with ACE inhibition may result in volume depletion, causing a decline in renal perfusion. As a consequence glomerular filtration rate, the primary determinant of renal function, decreases. Increasing tissue levels of ACE inhibitors with diuretics may achieve maximal cardioprotection. Notably, tissue ACE activity during therapy is strongly associated with the severity of organ damage. However, the decrease in renal function caused by addition of a diuretic to ACE inhibition may eventually have a detrimental impact on prognosis after myocardial infarction, as is discussed in the following section.

**Diuretics and long-term prognosis**

In chapters 4 and 5 it was shown that hydrochlorothiazide added to ACE inhibition caused a marked increase in plasma creatinine concentrations, indicating reduced glomerular filtration rate. Furthermore, renal interstitial fibrosis and tubular degeneration were seen in rats with myocardial infarction treated with the combination of HCTZ and the ACE inhibitor quinapril, but not quinapril monotherapy. Although a direct causal relation between the HCTZ-induced decrease in renal function and long-term survival was not shown, these observations indicate that HCTZ added to ACE inhibition decreases renal function to an extent that could be associated with increased long-term mortality. It is firmly established that kidney function is negatively influencing long-term prognosis in patients with left ventricular dysfunction after myocardial infarction, but the mechanisms underlying this interaction are still
incompletely understood. It has been suggested that the relation between mild renal impairment and progression of cardiac disease in humans is non-causal, and that both are the consequence of traditional cardiovascular risk factors, such as atherosclerosis and hypertension\textsuperscript{18,19}. However, these confounding factors are not present in our experimental MI model. Thus, decreased GFR (reflected by increased plasma creatinine concentrations) itself may be a risk factor triggering development heart failure. Accordingly, unfavorable cardiac changes related to remodeling, such as cardiomyocyte dropout\textsuperscript{20}, increased cardiomyocyte/capillary ratios\textsuperscript{21}, and impaired energy metabolism\textsuperscript{22} have been observed in rats with (mild) renal impairment. Furthermore rats with mild renal impairment by nephrectomy showed reduced ischemia tolerance, via a yet unresolved mechanism, but independent of confounding effects of hypertension, sympathetic overactivity, and salt retention\textsuperscript{23}. Such effects of mild renal function could eventually result in unfavorable effects on mortality during prolonged follow-up. The studies described in this thesis suggest that in HCTZ added to ACE inhibition in experimental LV dysfunction improves intermediate parameters, but that on the long-term, these beneficial effects are offset. Thus, it deserves recommendation that further studies on the effects of diuretics and ACE inhibition on LV dysfunction as well as renal failure and hypertension involve hard end-points and have extended follow-up.

**Long-term cardiovascular protection by ACE inhibition**

In addition to direct cardiac effects, ACE inhibition has several beneficial effects on the structure and function of blood vessels that may at least partially underlie its cardioprotective effects. Increased peripheral vascular resistance, which is thought to be the combined result of endothelial dysfunction\textsuperscript{24,25} and increased myogenic tone of resistance arteries\textsuperscript{26}, is a hallmark of LV dysfunction. Although ACE inhibition is known to improve endothelial function, it is not undisputed which components of endothelium-dependent vasodilation are improved\textsuperscript{27-32}. These components include nitric oxide (NO), vasoactive prostanoids, and endothelium-derived hyperpolarizing factor (EDHF). Chapter 7 shows that development of endothelial dysfunction in rats with myocardial infarction was largely explained by a decline in EDHF-mediated endothelium-dependent vasorelaxation, and that ACE inhibition could restore this EDHF. Although the exact nature of EDHF is not completely elucidated, and may be $K^+\textsuperscript{33}$, electric signaling via gap junctions\textsuperscript{34}, or epoxyeicosatrienoic acids\textsuperscript{35}, all EDHFs exert their vasodilating effect through opening of $Ca^{2+}$-dependent $K^+$ ($K_{Ca}$) channels. Previous studies showed that EDHF contributes substantially to endothelium-dependent relaxation, not only in large conductance arteries, but also in coronary arteries and small resistance arteries\textsuperscript{36,37}. Our findings confirm the identification of EDHF as a potential therapeutic target to prevent the progression of left ventricular dysfunction\textsuperscript{38}. Accordingly, we showed that withdrawal of chronic ACE inhibition in rats with myocardial infarction was not only associated with accelerated development of left ventricular hypertrophy and reduced cardiac contractility, but most notably, a rapid development of marked endothelial dysfunction (chapters 6 and 7). This is in accordance with previous observations in patients with myocardial infarction, where ACE-I
withdrawal resulted in a high incidence of cardiac ischemic events\textsuperscript{39,40}. Endothelial dysfunction with increased tendency for coronary vasospasm and acute coronary thrombotic processes is associated with an increased risk for ischemic events. Thus endothelial dysfunction, rather than progression of heart failure\textsuperscript{41} appears a matter of concern during the early phase after abrupt cessation of ACE inhibition.

**Conclusion**

As far as animal studies can be extrapolated to man, it seems improbable that on the long-term dietary sodium restriction will substantially improve prognosis of patients with myocardial infarction treated with an optimal dose of ACE-I. Although addition of sodium restriction to ACE-I therapy did improve intermediate parameters in rats with myocardial infarction, treatment outcome was not altered. In contrast, diuretic treatment improved early chronic survival and cardiac function. The underlying mechanism was not RAAS activation, but either potentiation of ACE inhibition via a pharmacokinetic interaction, or a direct effect of HCTZ, independent of sodium status or ACE inhibition. However, on the long term, these beneficial effects of combining ACE inhibition with diuretic therapy were abolished, presumably as a result of adverse renal effects of chronic combination therapy.

Based on our results, patients with LV dysfunction after MI may benefit from addition of a diuretic to ACE inhibition therapy, but loss of renal function may be a drawback during prolonged treatment. Combination treatment for a limited period of time (weeks to months) after MI is a strategy deserves consideration.

ACE inhibition after MI remains effective during extended follow-up, and abrupt cessation - even for brief periods - should be avoided. During the early phase after withdrawing ACE inhibition, endothelial dysfunction and a subsequent risk for cardiac ischemia, rather than cardiac remodeling, appears a matter of concern.

**References**


Summary

Left ventricular (LV) dysfunction is characterized by a progressive loss of cardiac pump function, which eventually leads to the clinical syndrome of chronic heart failure (CHF). Heart failure is associated with high morbidity and mortality. The incidence of heart failure has increased during the last decades, mainly because improved survival after acute myocardial infarction.

Renin angiotensin aldosterone system (RAAS) activation plays a major role in the progression of left ventricular dysfunction towards chronic heart failure. Angiotensin-converting enzyme (ACE) inhibition therapy improves cardiac function and reduces morbidity and mortality.

Although ACE-inhibition slows the gradual progression of myocardial dysfunction towards overt CHF, it does not prevent it. In order to reach maximal therapy response to ACE inhibition a low sodium intake may be required. The expected underlying mechanism was that an activated RAAS – i.e. elevated renin production – induced by sodium restriction is required for an optimal therapeutic response to ACE inhibition. Hence, the first main subject of this thesis was to study intervention with the sodium balance in order to optimize ACE-I therapy. In chapter 2 we describe the effects of dietary salt restriction on ACE inhibitor treatment in rats with myocardial infarction, after 10 weeks of follow-up. Whereas dietary salt restriction alone did not worsen or improve any of the studied parameters, it augmented left ventricular –but not renal or plasma- ACE inhibition with zofenopril. This further reduction of ACE activity was associated with a more potent anti-hypertrophic effect of the drug. Although LV hypertrophy reduction with zofenopril was improved by dietary salt restriction, we did not find a further improvement of in vitro cardiac function.

We subsequently studied whether on the long term dietary salt restriction may improve the outcome of long term ACE inhibition therapy. Therefore, we studied mortality during a period of 14 months, and in vivo cardiac function. The results are described in chapter 3, and show that during 14 months of treatment with the ACE inhibitor quinapril dietary sodium restriction did not improve survival or cardiac function in rats with myocardial infarction. Based on these results, we question the benefit of dietary sodium restriction during long-term ACE inhibition for post-infarct left ventricular dysfunction. More encouraging results were obtained with addition of a diuretic (hydrochlorothiazide) to quinapril treatment. This pharmacological strategy to induce a negative sodium balance was also studied, as it is easier to maintain for the patient, and already commonly used in the cardiologic practice to reduce symptoms of fluid retention. We showed an improvement in survival and cardiac function during the first 8 months of follow-up. However, towards the end of follow-up period (14 months), the beneficial effects of hydrochlorothiazide waned off. This discrepancy between early beneficial effects and loss of benefit towards the end of long-term treatment is further discussed below, but first we focused on short-term effects of hydrochlorothiazide on ACE-I therapy.

In chapter 4 we investigated whether the (early) benefits of adding hydrochlorothiazide to ACE inhibition could be explained by a pharmacokinetic interaction. We observed
that indeed the diuretic caused accumulation of two different ACE inhibitors. The hydrophilic ACE inhibitor lisinopril accumulated in plasma, whereas the lipophilic ACE inhibitor zofenopril accumulated mainly in heart and kidney tissue. We showed that the most likely mechanism is a hydrochlorothiazide-induced volume depletion, either directly or via a GFR decrease leading to reduction in renal clearance of the ACE inhibitors. The potential risk of this loss of kidney function is the main issue in chapter 5. Here we show that combining hydrochlorothiazide with quinapril caused an increase in plasma creatinine, which indicates decreased renal function. Furthermore we showed that increased plasma creatinine concentrations measured after 4 months of treatment were significantly associated with increased mortality in rats with myocardial infarction towards 14 months of follow-up. Furthermore, histopathology showed that addition of hydrochlorothiazide to quinapril in rats with myocardial infarction caused tubular degeneration as well as inflammation and fibrotic lesions in renal proximal tubular interstitium. From this study we conclude that during long-term treatment post-MI combining ACE inhibition with a diuretic can causes renal abnormalities, which could cancel out the early beneficial effects of addition of a diuretic to ACE inhibitor therapy.

Second main topic of this thesis was to study the consequences of ACE inhibitor withdrawal on cardiac function and neurohormones, and endothelial function. In contrast to the well-studied beneficial effects of ACE inhibition therapy itself, remarkably little has been published about the consequences of its withdrawal. In chapter 6 we report progressive left ventricular hypertrophy and activation of the renin-angiotensin-aldosterone system after 4 and 6 weeks of ACE inhibitor withdrawal. Secondly, we found that substantial endothelial dysfunction, which plays a central role in the pathophysiology of heart failure, developed within 4 weeks after cessation of therapy.

In chapter 7, we studied the involvement of nitric oxide (NO) and endothelium-derived hyperpolarizing factor (EDHF) in the vascular effects of the ACE-I quinapril and its withdrawal. We showed that long-term ACE inhibition in rats with myocardial infarction markedly improved non-NO/prostanoid-mediated (i.e. EDHF-mediated) endothelium-dependent vasorelaxation. Within four weeks after treatment withdrawal this beneficial effect completely disappeared. These findings highlight the potential importance of EDHF impairment in development of endothelial dysfunction after myocardial infarction, and the possibility to improve EDHF-mediated vasodilation with chronic ACE inhibitor therapy.

The observed alterations after withdrawing long-term post-MI quinapril treatment in the present study may account for an increased risk for ischemic events. By that our findings highlight the potentially harmful effects associated with abrupt discontinuation of long-term post-MI ACE inhibition, and imply careful clinical consideration in this matter.

Chapter 8 provides a final overview on the issue of sodium depletion to augment tissue ACE inhibition. Sodium restriction or diuretic therapy per se does not influence the progression of LV dysfunction into chronic heart failure, with the exception of aldosterone receptor antagonists. Furthermore, it seems improbable that on the long-
term sodium depletion will substantially improve prognosis of patients with myocardial infarction treated with ACE inhibition in an optimal dose. Although addition of sodium restriction improved intermediate parameters in rats with myocardial infarction, treatment outcome was not altered. Diuretic treatment improved early chronic survival and cardiac function. Thus long-term treatment with this diuretic in combination with ACE inhibition after myocardial infarction may be safe, as far as animal experiments can be extrapolated to humans. As long-term survival was similar in rats treated with ACE-I alone and combined with hydrochlorothiazide, the balance between beneficial and adverse effects of adding diuretics to ACE inhibition therapy thus far ends up undecided.