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Beneficial effects of add-on hydrochlorothiazide in rats with myocardial infarction optimally treated with quinapril

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Abstract

Background: The antihypertensive and renoprotective effects of ACE inhibitor (ACEi) therapy are enhanced by inducing a negative sodium balance. Whether this strategy also improves outcome of chronic ACEi treatment after myocardial infarction (MI) is unknown. Therefore, we investigated whether hydrochlorothiazide (HCTZ) or dietary sodium restriction further improves survival in ACEi-treated rats with MI.
Methods: MI was induced by coronary ligation. After 2 weeks rats were randomised to quinapril (QUI), HCTZ added to quinapril (QUI+HCTZ), or low sodium diet added to quinapril (QUI+LS). Survival was monitored for 62 weeks, after which left ventricular (LV) pressures were measured and blood for neurohumoral characterisation was collected. A separate group of rats, subjected to the same procedure, was evaluated after 35 weeks.
Results: After 62 weeks, mortality was comparable in all groups. However, survival was improved by HCTZ until 35 weeks. This effect on survival was paralleled by decreased proteinuria and LV end-diastolic pressures in QUI+HCTZ rats at 35, but not 62 weeks. Plasma renin activity was significantly decreased in QUI+HCTZ rats at 35 weeks. Contrary to HCTZ, LS added to QUI caused no benefit.
Conclusions: Adding HCTZ, but not LS, to quinapril improved survival, neurohumoral status, and proteinuria during the early chronic phase of experimental post-MI LV dysfunction. Since no adverse effects were observed, HCTZ may safely be used to improve ACEi therapy.

Keywords: ACE inhibition; Experimental myocardial infarction; Rat; Diuretic; Renin angiotensin system

1. Introduction

The progression of left ventricular (LV) dysfunction towards overt chronic heart failure (CHF) after myocardial infarction (MI) is associated with progressive cardiac remodelling. Renin angiotensin aldosterone system (RAAS) activation plays a central role in this process, and blocking the RAAS with angiotensin-converting enzyme inhibitors (ACEi) effectively reduces remodelling and prolongs survival after MI. Still, prognosis post-MI is grim, and optimisation of therapy is necessary [1,2].

Antihypertensive and renoprotective effects of ACEi can be enhanced by dietary sodium restriction or co-treatment with diuretics [3–5]. For heart failure treatment, this has not been investigated. Sodium depletion itself has never been shown to affect the progression of LV dysfunction in terms of LV remodelling [6–9] or LV hemodynamic parameters [10]. However, induction of a negative sodium balance may provide a strategy to enhance the therapeutic efficacy of ACEi in heart failure. We previously showed that sodium restriction added to ACEi treatment further attenuated LV hypertrophy in MI-rats, which was associated with augmented inhibition of LV tissue ACE activity [11]. Whether this also results in improved cardiac function and reduced mortality was addressed in the current study. We evaluated

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the long-term effects of additional diuretic treatment or a low sodium diet on mortality, cardiac function, neurohumoral activity, and urinary protein excretion in rats with experimental MI on optimal ACEi therapy. We hypothesised that diuretics and dietary sodium restriction: 1) augment the beneficial effects of ACEi therapy and thus positively affect cardiac function and survival in rats with MI, and 2) exert no adverse effects and can be safely applied in post-MI ACEi therapy.

2. Methods

2.1. Study design

The investigation conforms to the Guide for the Care and Use of Laboratory Animals (Published by the US National Institutes of Health, NIH publication No. 85-23, revised 1996). The animal research committee of the University of Groningen approved this study protocol.

Male, Sprague Dawley rats (Harlan, Zeist, The Netherlands), weighing 280±25 g were subjected to coronary ligation as previously described [12,13]. Since the study was aimed at the chronic phase after myocardial infarction, and not at interfering with the early healing process and scar formation, treatment was started 14 days post-MI. Rats were randomly assigned to: quinapril alone (QUI), quinapril+hydrochlorothiazide (QUI+HCTZ), quinapril+-low sodium (QUI+LS). Since HCTZ or LS alone do not affect post-MI LV remodelling and function [6–11], we did not include treatment arms on only HCTZ or LS. As the effects of ACEi on MI rats are well established, we also refrained from including a non-treated MI-group in the survival study.

Quinapril (15 mg kg^{-1} day^{-1}) was mixed through food (Hope Farms, Woerden, The Netherlands). This dose results in optimal ACEi therapy [14–16]. HCTZ (50 mg kg^{-1} day^{-1}) was dissolved in drinking water. This dose causes an increase in diuresis and RAAS activation, but no blood pressure reduction in normotensive rats [9]. The LS-group was fed with food pellets containing 0.05% NaCl instead of 0.3% (normal diet) (LS-diet; Hope Farms, Woerden, The Netherlands). To ensure constant drug intakes during the entire study period, concentrations of quinapril and HCTZ were adjusted weekly. This was done by measuring food/water intake and average body weight per cage weekly, and calculating the required drug concentration in food and water (per cage) for the week after. Rats were fed ad libitum, and housed group-wise in clear polyethylene cages in temperature (22 °C)- and humidity (50%)-controlled rooms with a 12 h light/dark cycle.

2.2. Study 1: 62 weeks survival

Animals surviving surgical procedures (159 out of 320) were allocated to one of three active treatment groups, and monitored—in a blinded fashion—until death or for 62 weeks after onset of therapy. Use of colour-tags ensured appropriate housing and treatment by caretakers. Cages were checked for dead animals at least once daily; tissues of dead rats were collected, weighed and stored for analysis.

At 17, 35 and 52 weeks of treatment 24 h urine samples were collected for measurement of total urinary protein using a nephelometer (Dade Behring Diagnostic, Marburg, Germany). After the 62-week follow-up period, subgroups of randomly chosen surviving rats were sacrificed for assessment of LV function and neurohumoral activity.

2.3. Study 2: 35 weeks of treatment

In total 90 rats were used for this protocol, designed to study neurohormones and cardiac function during the course of the study period in relation to untreated MI rats. Rats were operated and treated according to the same procedures as in the above study, except that they were sacrificed and studied at 35 weeks after onset of treatment.

2.4. Assessment of cardiac function

Rats were anaesthetised with isoflurane (2%) in a mixture of O_2 and N_2O (1:2), the carotid artery was cannulated and a pressure tip catheter (Micro-Tip 3French, Millar instruments, Houston TX, USA) advanced into the LV. After registration of LV systolic and diastolic pressures (LVSP and LVEDP), and maximal rates of increase and decrease in LV pressure (+dP/dt and −dP/dt), the catheter was retracted into the aortic arch, and arterial pressures and heart rate were recorded. Subsequently, arterial blood and tissues were collected for further analysis.

2.5. Neurohumoral measurements

Arterial blood was anti-coagulated with EDTA and N-terminal atrial natriuretic peptide (N-ANP), plasma renin activity, and aldosterone, were measured in the plasma as previously described [17]. Plasma for ACE activity determination was collected separately, and not anti-coagulated with EDTA. ACE activity in the plasma and spared myocardial tissue was determined as described before [12].

2.6. Tissue collection and histology

Hearts were rinsed with ice cold NaCl (0.9%), and the atria and right ventricle were removed on ice for determination of LV weights. The apical 1/3 part of the LV was cut off, spared and infarcted tissues were separated, and frozen in liquid nitrogen for measurement of left ventricular ACE activity. The mid-ventricular slice of the LV was stored in 2% paraformaldehyde for

Table 1
General characteristics of rats included in the survival study, general characteristics and hemodynamics of MI rats after chronic ACEi therapy, and additional effects of HCTZ or dietary sodium restriction after 35 and 62 weeks

		MI control	QUI	QUI+HCTZ	QUI+LS
Survival study:					
n (start treatment)		–	44	45	35
Infarct size (% of LV)		–	33.7±1.1	32.0±1.1	34.8±1.4
Mortality (%)					
	wk35	–	11	0*	3
	wk62	–	23	20	26
Sacrificed rats:					
n	wk35	4	6	5	5
	wk62	–	11	12	10
Infarct size (% of LV)	wk35	26.9±2.5	24.7±1.0	28.2±1.1	29.3±2.6
	wk62	–	34.0±2.2	32.7±1.3	36.7±1.6
Hemodynamic parameters:					
MAP (mmHg)	wk35	98.3±7.2	72.1±3.0*	71.5±4.4*	71.6±3.6*
	wk62	–	71.3±4.5	72.5±2.6	70.0±3.1
LVEDP (mmHg)	wk35	14.0±2.3	10.4±1.8	7.3±2.5#	10.0±2.5
	wk62	–	12.4±2.6	12.4±0.9	12.8±1.1
+dP/dt (10^3 mmHg s^{-1})	wk35	10.3±0.8	8.4±0.2*	8.7±0.5*	8.9±0.4
	wk62	–	8.5±0.3	8.1±0.4	7.8±0.2
−dP/dt (10^3 mmHg s^{-1})	wk35	−8.6±0.6	−6.9±0.6*	−7.6±0.3	−7.4±0.4
	wk62	–	−7.1±0.3	−6.9±0.3	−6.6±0.2
Electrolytes:					
Plasma Na^+ (mmol L^{-1})	wk35	142.8±4.4	137.4±0.3	136.6±0.5*	134.5±4.7*
Plasma K^+ (mmol L^{-1})	wk35	3.9±0.2	4.4±0.1*	4.4±0.2*	4.5±0.1*

* Indicates $p<0.05$ versus MI control.
\# LVEDP at 35 weeks: QUI+HCTZ $p=0.07$ versus control; wk: week of treatment.

histologic assessment of infarct size on slices stained with Sirius Red/Fast Green, as described previously [12]. Infarct size was determined as percentage of LV circumference. The mid-ventricular section provides adequate estimation of total LV infarct size [18]. Only rats with MI sizes larger than 20% of LV were included for analysis, since smaller infarcts do not result in LV dysfunction [19,20].

2.7. Statistical methods

The survival study was designed to detect a difference of 20% in 1-year mortality with a power of 0.80, with an expected mortality of 60% in the control group that received quinapril only, based on the early captopril studies [21]. Survival analysis was done using log rank analysis with pairwise comparison over strata. Functional

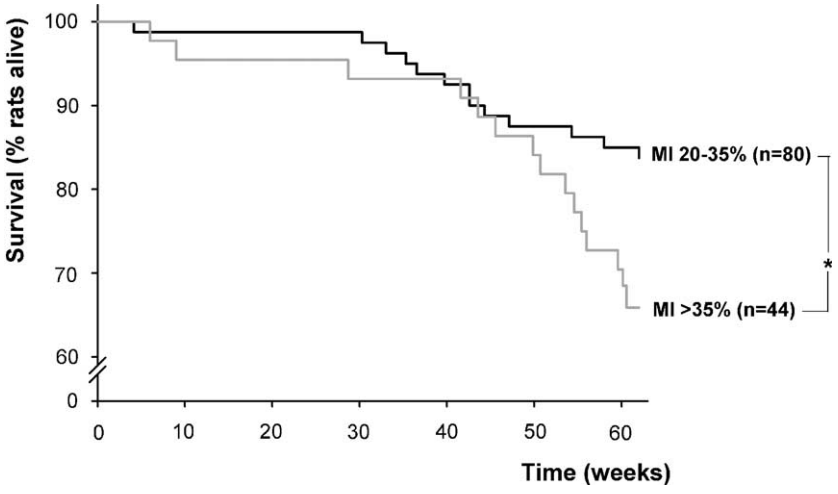

Fig. 1. Influence of infarct size on survival after MI in rats treated with quinapril, irrespective of co-treatment. Groups were divided into moderate (20–35%, $n=80$) and large infarction (>35%, $n=44$). *$p<0.05$ as indicated.

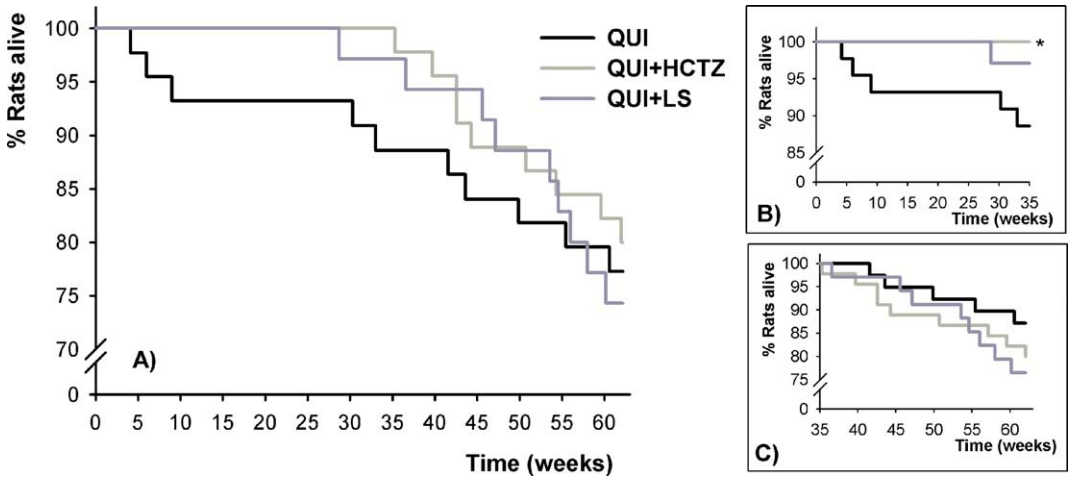

Fig. 2. Survival after experimental MI in rats treated with quinapril, and effects of additional hydrochlorothiazide or low sodium diet. A) Survival after 35 weeks was significantly improved by HCTZ added to quinapril, as denoted by *. B) and C) exhaustion analysis of mortality between week 0–35 and 35–62, with number of rats alive after 35 weeks reset to 100% in C).

and neurohumoral parameters were compared using one-way analysis of variances (ANOVA) with least square difference post hoc analysis for multiple comparisons in case of normal distribution of data. Otherwise, a Kruskal–Wallis test was used. Differences were considered significant at the level of 0.05 (two tailed). Bodyweights, food and water intakes were analysed with ANOVA for repeated measurements (general linear model). Data are presented as

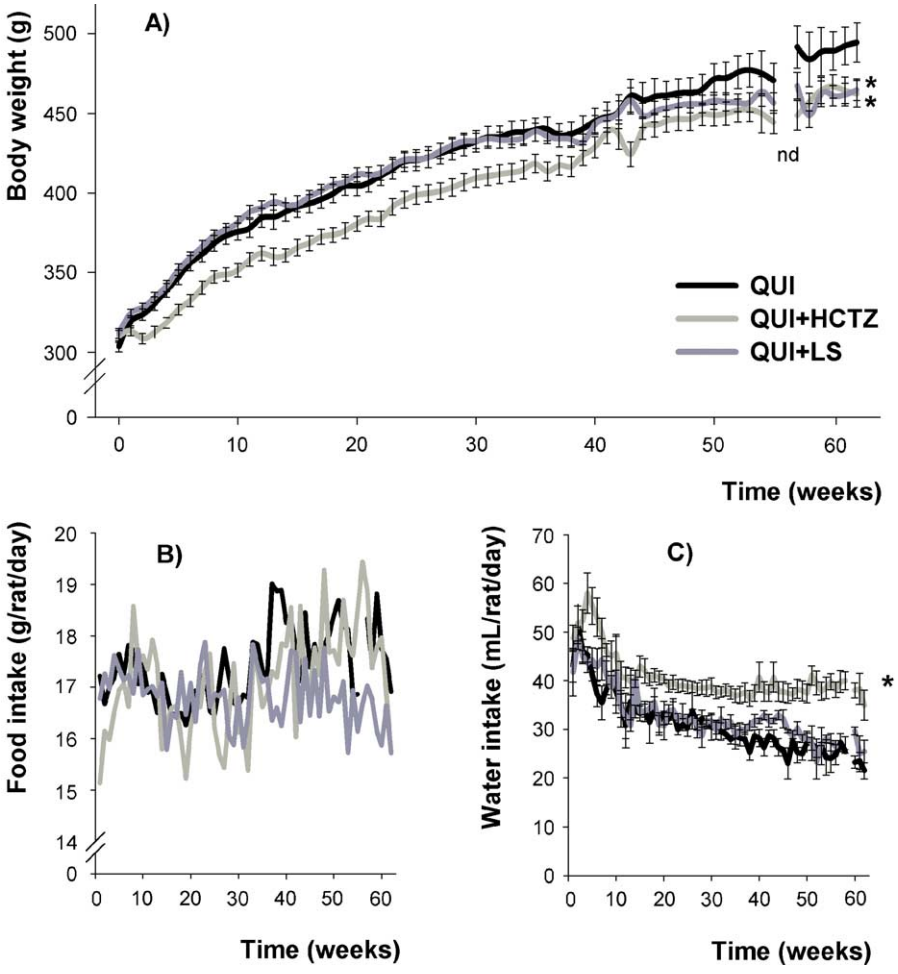

Fig. 3. Body weights, water and food intake of MI rats treated with quinapril (QUI), and effects of additional HCTZ or dietary sodium restriction. Error bars in C) are omitted for reasons of clarity. nd: no data. *$p<0.05$ vs. QUI.

Table 2
Organ weights of MI rats after long-term quinapril therapy, and the additional effects of hydrochlorothiazide therapy or dietary sodium restriction after 35 and 62 weeks

		MI control	QUI	QUI+HCTZ	QUI+LS
Body weight (g)	wk35	520±16	457±8*	440±16*	460±19*
	wk62	–	487±19	452±10	466±11
Heart weight (mg g^{-1})	wk35	3.51±0.09	2.98±0.07*	3.04±0.12*	2.96±0.10*
	wk62	–	3.27±0.10	3.26±0.08	3.13±0.07
Left ventricle weight (mg g^{-1})	wk35	2.38±0.04	1.97±0.05*	2.00±0.10*	1.90±0.09*
	wk62	–	2.03±0.04	2.07±0.05	2.06±0.04

All organ weights were corrected for body weight.
* Indicates $p<0.05$ versus MI control.

means±SEM in case of normal distribution, otherwise in boxplots.

3. Results

3.1. Study 1: 62 weeks survival

Of the 159 rats studied, 35 were excluded from survival analysis: MI-size was <20% in 26 rats, infarct size could not be determined in 3 rats; 6 rats developed tumours and were sacrificed prematurely. Remaining group sizes at the onset of treatment were n=44 for quinapril, n=45 for quinapril+HCTZ, and n=35 for quinapril+low sodium diet. Infarct sizes were evenly distributed over the different treatment groups (Table 1).

Comparison of subgroups based on infarct size irrespective of treatment showed that total mortality was significantly higher in rats with extensive infarcts (>35% of LV) than in rats with moderate (20–35% of LV) infarcts (Fig. 1, p=0.02). This confirms that mortality in this study is related to myocardial infarction, in a MI-size-dependent way. The time course of mortality suggests different phases, with a low mortality during the first 35–40 weeks of treatment, followed by a steep increase in mortality in rats with large MI in the late phase of follow-up.

Survival was similar in the three treatment groups after the complete follow-up period of 62 weeks (Fig. 2A). However, the data suggest two different periods with distinct effects of additional treatment (Fig. 2B and C). During the first 35 weeks survival was significantly improved by additional hydrochlorothiazide (Table 1, Fig. 2B). Mortality in the groups treated with quinapril only and quinapril+HCTZ was parallel between weeks 35 and 62 (Fig. 2C). Survival in the group receiving a low sodium diet in addition to quinapril was intermediate and never significantly different from the other groups.

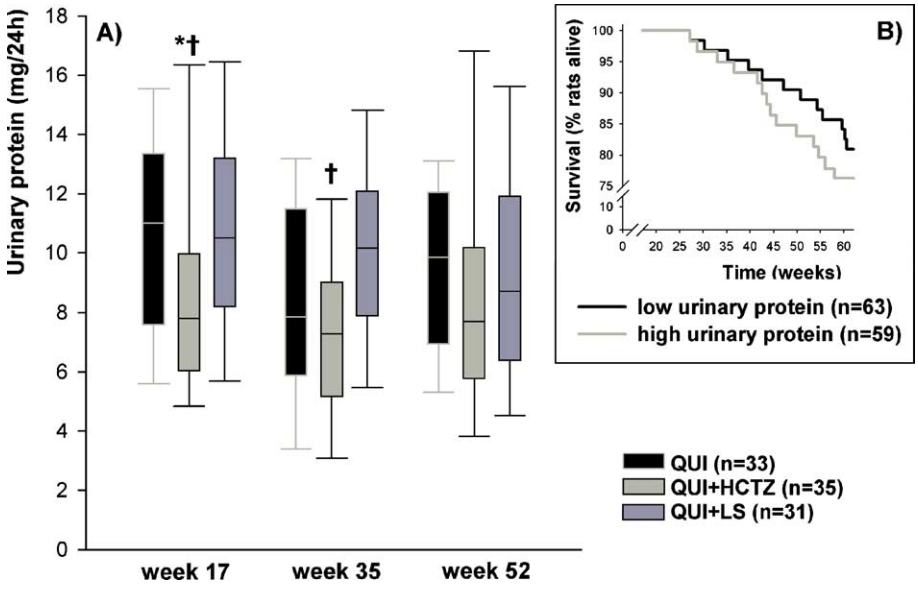

Fig. 4. Urinary protein excretion during chronic quinapril therapy, and the effects of additional hydrochlorothiazide or dietary sodium restriction. A) Bar graphs showing significantly decreased proteinuria at 17 and 35 weeks in QUI+HCTZ rats, and no differences at 52 weeks; only rats alive at 52 weeks were included in the analysis to avoid bias by mortality. Urine production was comparable and decreased over time in all groups: at 17 weeks 27±1, 27±1, and 29±2; at 35 weeks 17±2, 18±1, and 23±2; at 52 weeks 15±1, 20±1, and 18±1 mL for QUI, QUI+HCTZ, and QUI+LS, respectively. B) Survival curves suggesting predictive value of urinary protein levels. Rats were divided into 2 groups: below and above total average 24-h protein excretion for each treatment group. The group with lower urinary protein excretion showed a trend towards improved survival (no significance). *p<0.05 vs. QUI, †p<0.05 vs. QUI+LS.

Body weight gain was significantly reduced during the first 3 weeks in rats treated with quinapril+HCTZ. Thereafter, the difference remained approximately 20 g compared to quinapril only throughout the study (Fig. 3A). The reduced weight gain in rats on quinapril+HCTZ was paralleled by a combination of markedly increased drinking and slightly decreased food intake (Fig. 3B and C). Water intake remained significantly increased in the HCTZ group during the entire treatment period (Fig. 3C). Body weights in rats additionally receiving low sodium diets as compared to quinapril only were almost identical during the first 45 weeks of treatment, but became significantly lower thereafter.

After 62 weeks of treatment, no differences in mean arterial blood pressure (MAP), cardiac function (LV systolic and diastolic pressures, +dP/dt and −dP/dt), and LV hypertrophy (cardiac weights) were seen (Tables 1 and 2).

At comparable urine production during all time points (see legend Fig. 4), urinary protein excretion was significantly lower in rats treated with quinapril+HCTZ than in rats receiving quinapril only at 17, but not at 35 and 52 weeks. Contrary to HCTZ, dietary sodium restriction did not influence urinary protein excretion. Interestingly, comparison of survival curves of MI-rats based on urinary protein excretion at week 17 irrespective of treatment, suggests a trend of improved survival in the group with protein excretion below average (Fig. 4B).

3.2. Study 2: 35 weeks treatment

Mortality within 24 h after MI-induction in this group was 38%. Of the remaining 53 MI-rats that entered the study, 33 were excluded from analysis for infarct sizes

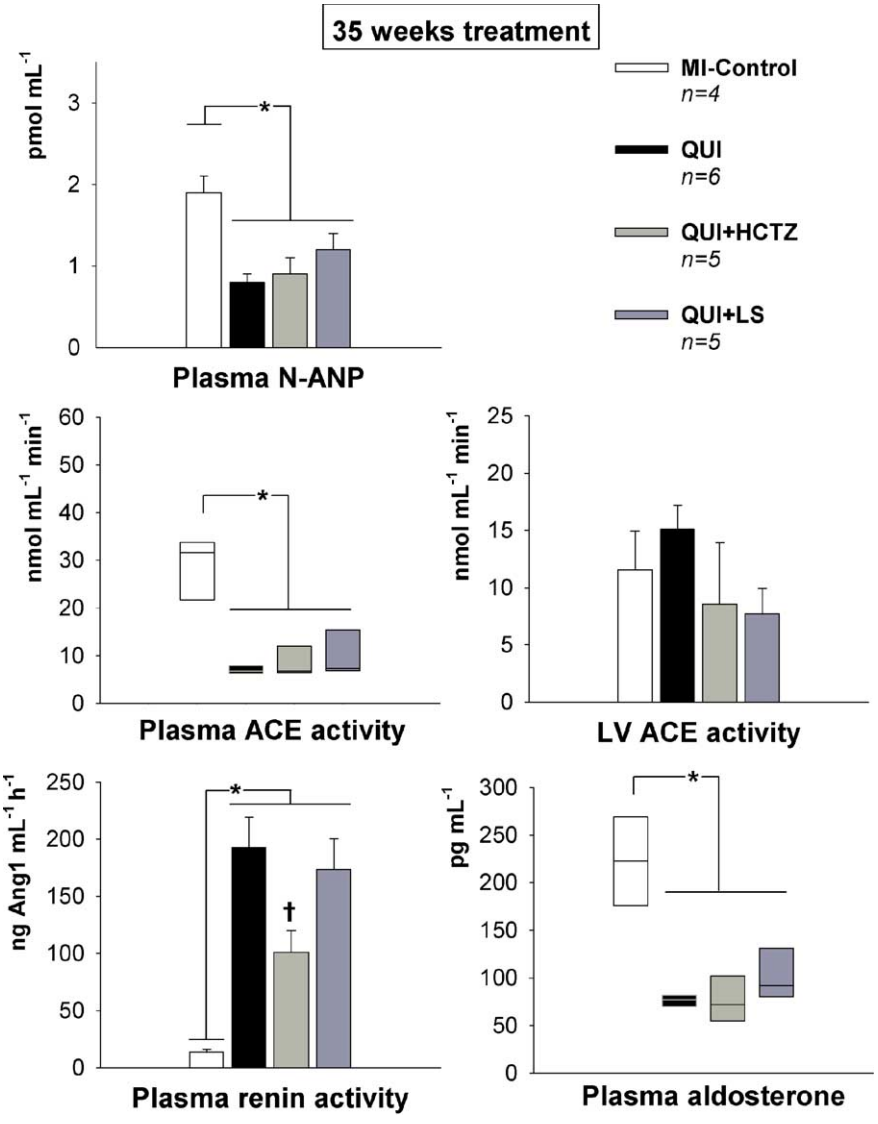

Fig. 5. Circulating and tissue RAAS after 35 weeks treatment with QUI, and effects of additional hydrochlorothiazide or low sodium diet. *p<0.05 vs. MI untreated, †p<0.05 vs. QUI.

below 20%, leaving the following groups: n=4 untreated MI controls, n=6 for QUI, n=5 for QUI+HCTZ and n=5 for QUI+LS. MI-sizes were similar in all groups in study 2, but on average slightly smaller than in study 1 (Table 1).

After 35 weeks, mean arterial blood pressure was markedly decreased by quinapril treatment, but not further affected by hydrochlorothiazide or dietary sodium restriction. LVEDP in rats treated with HCTZ in addition to quinapril was decreased by 50% compared with untreated MI controls and 30% compared with quinapril alone (Table 1). Both +dP/dt and −dP/dt were similar in the 3 groups treated with quinapril. At 35 weeks, heart and left ventricular weights were significantly reduced by quinapril, and additional hydrochlorothiazide or low sodium diet (Table 2) did not modify this reduction.

3.3. Neurohormones in studies 1 and 2

Neurohormones were studied after 35 and 62 weeks of treatment (Figs. 5 and 6). At 35 weeks, plasma N-ANP (indicative for LV stress), ACE activity, and aldosterone were significantly decreased in quinapril-treated rats compared to untreated MI-rats. From 35 to 62 weeks, N-ANP, ACE activity, and aldosterone showed an increasing trend in all groups, suggesting progression of LV dysfunction despite ACE inhibition therapy. Additional treatment with hydrochlorothiazide or dietary sodium restriction did not modify these effects of quinapril, except for plasma aldosterone being significantly higher in rats co-treated with low sodium than with quinapril alone at 62 weeks. LV ACE activity was comparable in all groups both at 35 and 62 weeks of treatment. Quinapril caused a profound increase

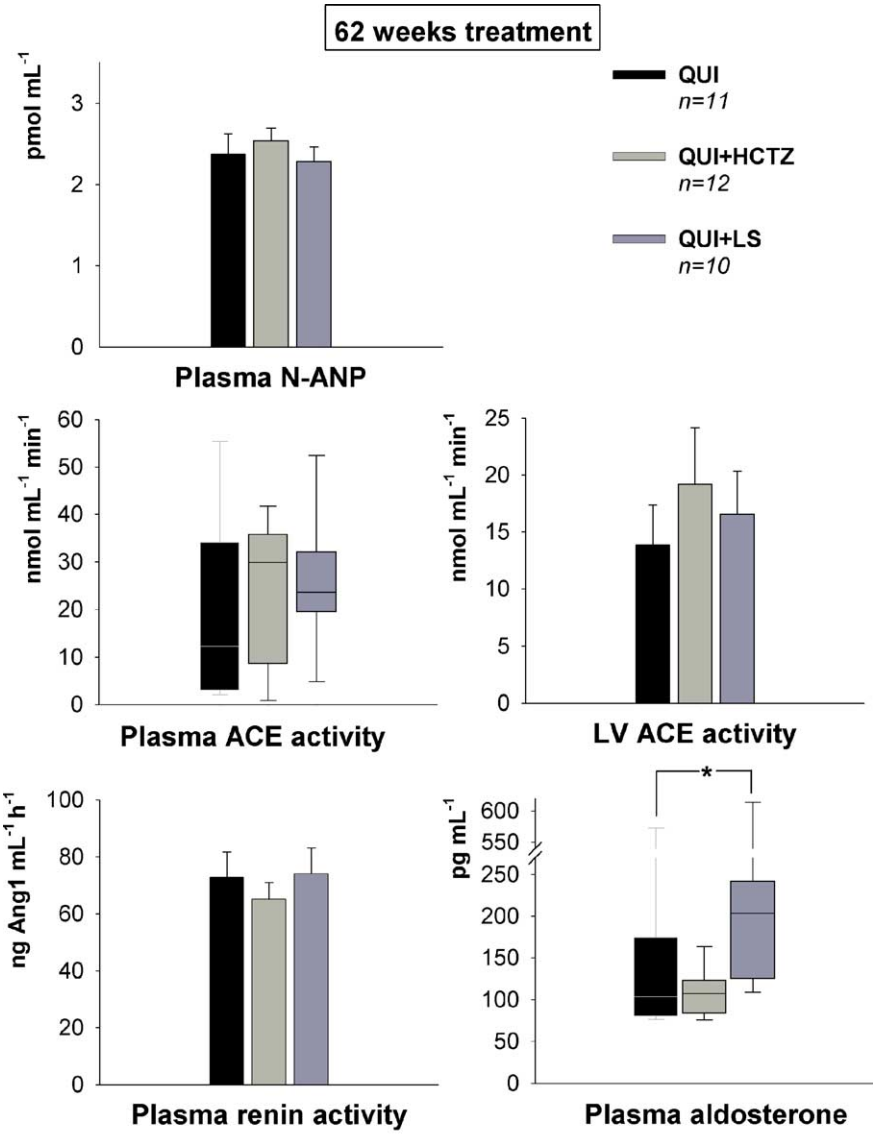

Fig. 6. Circulating and tissue RAAS after 62 weeks treatment, and effects of additional hydrochlorothiazide or low sodium diet. *p<0.05 vs. QUI.

in plasma renin activity at 35 weeks, which tended to be decreased again after 62 weeks treatment. Interestingly, this increase was markedly reduced after co-treatment with hydrochlorothiazide, but not with dietary sodium restriction. After 62 weeks, plasma renin activity no longer differed among the treatment groups.

Slightly increased plasma K^+ levels in quinapril-treated rats at 35 weeks were not affected by co-treatment. In contrast, plasma Na^+ concentrations were not significantly affected at 35 weeks in rats treated with quinapril alone, as compared to those untreated, but significantly decreased in those rats additionally treated with hydrochlorothiazide or low sodium—which is in accordance with our study aim to induce a negative sodium balance.

4. Discussion

The aim of this study was to investigate whether a negative sodium balance enhances cardioprotective effects of high-dose ACE inhibitor therapy after MI. We studied long-term effects of additional hydrochlorothiazide or dietary sodium restriction on survival, cardiac function, and neurohormones in rats with MI-induced LV dysfunction receiving quinapril.

4.1. Hydrochlorothiazide

Overall mortality during ACEi therapy was low compared to similar survival studies with experimental heart failure [21,22]. Since only high-dose ACEi treatment exerts a profound effect on long-term survival after MI [23], the low mortality rate in the present study indicates ACEi treatment in accordance with our aim: to study sodium depletion on top of optimal ACEi therapy.

Survival was not improved by HCTZ at the complete follow-up period of 62 weeks. However, when looking at the survival curves in Figs. 1 and 2 in more detail, different phases could be identified. Survival curves based on infarct size (Fig. 1) show two distinct phases: comparable mortality in rats with moderate and extensive MI in the early phase (± weeks 1–40), whereas curves diverged rapidly in the late phase (± weeks 40–62). Add-on HCTZ therapy significantly improved survival until 35 weeks, but had no beneficial effect on survival between weeks 35 and 62. Interestingly, several other animal studies on RAAS inhibition with long follow-up periods show a biphasic pattern as well [21,23,24]. Captopril only improved early survival in rats with large infarcts, but predominantly late survival in rats with moderate infarct sizes [21]. In a clinical setting, the beneficial effects of ACEi therapy with enalapril were most pronounced during the early treatment phase [25], and may decrease over time [26,27]. Taken together, these findings suggest different stages of post-MI dysfunction, both time- and infarct-size related, with distinct effects of ACEi treatment. It may hence be not surprising that in our study effects of additional HCTZ treatment follow these phases.

The exact mechanism underlying improvement of ACEi therapy with hydrochlorothiazide is not clear. As dietary sodium restriction had no beneficial effects, despite similar reduction in plasma Na^+ levels, favourable effects of HCTZ cannot be explained by sodium depletion only. A hemodynamic effect may play a role, since hydrochlorothiazide has direct vasodilator effects on vascular smooth muscle [28]. LVEDP after 35 weeks tended to be lower in rats treated with HCTZ on top of quinapril, which could reflect decreased venous return. Interestingly, parallel to the observed survival benefit at 35 but not 62 weeks, plasma renin activity after 35 but not 62 weeks of treatment was markedly reduced by HCTZ added to quinapril. From the point of view that diuretic therapy generally causes volume depletion and consequently increased plasma renin activity [9], this observation is surprising. An association between increased plasma renin activity and mortality in post-MI patients was shown in several studies [29–31]. The most important regulators of renin activity post-MI are decreased cardiac output and sympathetic activation, which both are associated with LV dysfunction and remodelling. Renin itself is not known to have direct cellular effects during post-infarct cardiac remodelling. However, HCTZ alone decreases sympathetic activation in rats with MI [7]. Thus, the decrease in plasma renin is likely to be an indicator for improved therapy outcome rather than a mediator of HCTZ effects.

In addition to improved survival during the first phase of the study, total urinary protein excretion was significantly decreased in rats treated with HCTZ. This further supports the early beneficial effects of additional HCTZ treatment. MI causes a progressive loss of renal function which affects prognosis [32]. Furthermore, in humans, urinary albumin excretion, even at non-proteinuric levels, is predictive for cardiovascular mortality [33]. As the degree of proteinuria reduction by ACE inhibition was found to be predictive for clinical long-term cardioprotection [34], we postulate that any reduction in urinary protein excretion may be considered to be indicative for improved ACEi therapy.

4.2. Dietary sodium restriction

Dietary sodium restriction did not positively affect quinapril treatment in this study, despite a reduction in plasma Na^+. We previously reported that addition of dietary sodium restriction to ACEi therapy resulted in significantly reduced cardiac hypertrophy and ACE activity [11]. However, this previous study was performed using zofenopril at a relatively lower (possibly sub-optimal) dose, which could explain differences between the two studies.

One concern is that dietary sodium restriction caused a twofold increase in plasma aldosterone levels in survivors at 62 weeks of treatment. This may be considered deleterious,

since high aldosterone levels were associated with clinical events in heart failure patients [29].

4.3. Clinical safety/feasibility

Although often applied in clinical practice, the use of diuretics in patients with LV dysfunction is controversial. Major concerns are severe hypotension and hypokalemia causing arrhythmia-associated deaths in patients with LV dysfunction [35]. Hence, we chose to treat rats with hydrochlorothiazide, which has less pronounced effects than loop diuretics, and indeed adding hydrochlorothiazide did not affect blood pressure or plasma K^+ levels. Thus, our results indicate that HCTZ may be safely added to long-term quinapril treatment.

In summary, we observed that additional hydrochlorothiazide treatment further improved survival during quinapril therapy in the first 35 weeks of chronic treatment after experimental MI in rats. This improvement in survival was associated with decreased urinary protein excretion, and improved parameters of left ventricular filling pressure and decreased RAAS activation. In contrast, dietary sodium restriction added to quinapril did not show any beneficial effects. As the rise in circulating aldosterone levels by dietary sodium restriction may be detrimental, the benefit of long-term dietary sodium restriction on post-MI outcomes could be questioned. Since no adverse effects of the combined therapy were observed, diuretics added to ACE inhibition can be a safe strategy to improve prognosis of post-MI LV dysfunction.

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References

[1] Pinto YM, van Geel PP, Alkfaji H, van Veldhuisen DJ, van Gilst WH. Dosing of ACE inhibitors in left ventricular dysfunction: does current clinical dosing provide optimal benefit? J Cardiovasc Pharmacol 1999;34(Suppl 1):S13–7.

[2] van Veldhuisen DJ, Genth-Zotz S, Brouwer J, Boomsma F, Netzer T, Man In 'T Veld AJ, et al. High- versus low-dose ACE inhibition in chronic heart failure: a double-blind, placebo-controlled study of imidapril. J Am Coll Cardiol 1998;32:1811–8.

[3] Navis G, de Jong P, Donker AJ, van der Hem GK, de Zeeuw D. Diuretic effects of angiotensin-converting enzyme inhibition: comparison of low and liberal sodium diet in hypertensive patients. J Cardiovasc Pharmacol 1987;9:743–8.

[4] Heeg JE, de Jong PE, van der Hem GK, de Zeeuw D. Efficacy and variability of the antiproteinuric effect of ACE inhibition by lisinopril. Kidney Int 1989;36:272–9.

[5] Buter H, Hemmelder MH, Navis G, de Jong PE, de Zeeuw D. The blunting of the antiproteinuric efficacy of ACE inhibition by high sodium intake can be restored by hydrochlorothiazide. Nephrol Dial Transplant 1998;13:1682–5.

[6] Hodsman GP, Sumithran E, Harrison RW, Johnston CI. Cardiac hypertrophy and salt status in chronic myocardial infarction in the rat: effects of enalapril versus salt restriction. J Cardiovasc Pharmacol 1988;12:467–72.

[7] Howes LG, Hodsman GP, Rowe PR, Johnston CI. Comparative effects of angiotensin converting enzyme inhibition (perindopril) or diuretic therapy on cardiac hypertrophy and sympathetic activity following myocardial infarction in rats. Cardiovasc Drugs Ther 1991;5:147–52.

[8] Seeland U, Kouchi I, Zolk O, Itter G, Linz W, Bohm M. Effect of ramipril and furosemide treatment on interstitial remodeling in post-infarction heart failure rat hearts. J Mol Cell Cardiol 2002;34:151–63.

[9] Kohzuki M, Kanazawa M, Yoshida K, Tsutsumi E, Yasujima M, Abe K, et al. Cardiomegaly and vasoactive hormones in rats with chronic myocardial infarction: long-term effects of chlorothiazide. Clin Sci (Lond) 1996;90:31–6.

[10] Sharpe N, Murphy J, Smith H, Hannan S. Treatment of patients with symptomless left ventricular dysfunction after myocardial infarction. Lancet 1988;1:255–9.

[11] Westendorp B, Schoemaker RG, Buikema H, de Zeeuw D, van Veldhuisen DJ, van Gilst WH. Dietary sodium restriction specifically potentiates left ventricular ACE inhibition by zofenopril, and is associated with attenuated hypertrophic response in rats with myocardial infarction. J Renin-Angiotensin-Aldosterone Syst 2004;5:27–32.

[12] Pinto YM, de Smet BG, van Gilst WH, Scholtens E, Monnink S, de Graeff PA, et al. Selective and time related activation of the cardiac renin–angiotensin system after experimental heart failure: relation to ventricular function and morphology. Cardiovasc Res 1993;27:1933–8.

[13] van Wijngaarden J, Pinto YM, van Gilst WH, de Graeff PA, de Langen CD, Wesseling H. Converting enzyme inhibition after experimental myocardial infarction in rats: comparative study between spirapril and zofenopril. Cardiovasc Res 1991;25:936–42.

[14] MacDonald JR, Susick Jr RL, Pegg DG, Dominick MA. Renal structure and function in rats after suprapharmacologic doses of quinapril, an angiotensin-converting enzyme inhibitor. J Cardiovasc Pharmacol 1992;19:282–9.

[15] Schaison FH, Fernando Ramirez-Gil J, Ciferri S, Bernard M, Baudin B, Mougenot N, et al. Acute and long-term dose-response study of quinapril on hormonal profile and tissue angiotensin-converting enzyme in Wistar rats. J Cardiovasc Pharmacol 1996;28:11–8.

[16] Kaplan HR, Taylor DG, Olson SC, Andrews LK. Quinapril—a preclinical review of the pharmacology, pharmacokinetics, and toxicology. Angiology 1989;40:335–50.

[17] van Veldhuisen DJ, Boomsma F, de Kam PJ, Mani V, Crijns HJ, Hampton JR, et al. Influence of age on neurohormonal activation and prognosis in patients with chronic heart failure. Eur Heart J 1998;19:753–60.

[18] Nelissen-Vrancken HJ, Kuizinga MC, Daemen MJ, Smits JF. Early captopril treatment inhibits DNA synthesis in endothelial cells and normalization of maximal coronary flow in infarcted rat hearts. Cardiovasc Res 1998;40:156–64.

[19] Schoemaker RG, Debets JJ, Struyker-Boudier HA, Smits JF. Delayed but not immediate captopril therapy improves cardiac function in conscious rats, following myocardial infarction. J Mol Cell Cardiol 1991;23:187–97.

[20] Pfeffer MA, Pfeffer JM, Fishbein MC, Fletcher PJ, Spadaro J, Kloner RA, et al. Myocardial infarct size and ventricular function in rats. Circ Res 1979;44:503–12.

[21] Pfeffer MA, Pfeffer JM, Steinberg C, Finn P. Survival after an experimental myocardial infarction: beneficial effects of long-term therapy with captopril. Circulation 1985;72:406–12.

[22] Mulder P, Boujedaini H, Richard V, Henry JP, Renet S, Munter K, et al. Long-term survival and hemodynamics after endothelin—a receptor antagonism and angiotensin-converting enzyme inhibition in rats with chronic heart failure: monotherapy versus combination therapy. Circulation 2002;106:1159–64.
[23] Wollert KC, Studer R, von Bulow B, Drexler H. Survival after myocardial infarction in the rat: role of tissue angiotensin-converting enzyme inhibition. Circulation 1994;90:2457–67.
[24] Marie C, Mossiat C, Gros C, Schwartz JC, Lecomte JM, Bralet J. Effect of long-term therapy with fasidotril, a mixed inhibitor of neprilysin and angiotensin-converting enzyme (ACE), on survival of rats after myocardial infarction. Cardiovasc Res 1999;41:544–53.
[25] Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial Study Group. Circulation 1990;82:1730–6.
[26] Swedberg K, Kjekshus J, Snapinn S. Long-term survival in severe heart failure in patients treated with enalapril. Ten year follow-up of CONSENSUS I. Eur Heart J 1999;20:136–9.
[27] Shieh FK, Kotlyar E, Sam F. Aldosterone and cardiovascular remodelling: focus on myocardial failure. J Renin-Angiotensin-Aldosterone Syst 2004;5:3–13.
[28] Pickkers P, Hughes AD, Russel FG, Thien T, Smits P. Thiazide-induced vasodilation in humans is mediated by potassium channel activation. Hypertension 1998;32:1071–6.
[29] Vantrimpont P, Rouleau JL, Ciampi A, Harel F, de Champlain J, Bichet D, et al. Two-year time course and significance of neuro-humoral activation in the Survival and Ventricular Enlargement (SAVE) Study. Eur Heart J 1998;19:1552–63.
[30] Rouleau JL, Packer M, Moye L, de Champlain J, Bichet D, Klein M, et al. Prognostic value of neurohumoral activation in patients with an acute myocardial infarction: effect of captopril. J Am Coll Cardiol 1994;24:583–91.
[31] Francis GS, Cohn JN, Johnson G, Rector TS, Goldman S, Simon A. Plasma norepinephrine, plasma renin activity, and congestive heart failure. Relations to survival and the effects of therapy in V-HeFT II. The V-HeFT VA Cooperative Studies Group. Circulation 1993;87: VI40–8.
[32] Hillege HL, van Gilst WH, van Veldhuisen DJ, Navis G, Grobbee DE, de Graeff PA, et al. Accelerated decline and prognostic impact of renal function after myocardial infarction and the benefits of ACE inhibition: the CATS randomized trial. Eur Heart J 2003;24:412–20.
[33] Hillege HL, Janssen WM, Bak AA, Diercks GF, Grobbee DE, Crijns HJ, et al. Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardio-vascular risk factors and cardiovascular morbidity. J Intern Med 2001;249:519–26.
[34] de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, et al. Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. Circulation 2004;110:921–7.
[35] Cooper HA, Dries DL, Davis CE, Shen YL, Domanski MJ. Diuretics and risk of arrhythmic death in patients with left ventricular dysfunction. Circulation 1999;100:1311–5.