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Heart failure development in rats with ascending aortic constriction and angiotensin-converting enzyme inhibition

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1 It remains unknown whether angiotensin-converting enzyme (ACE) inhibition can prevent heart failure in rats with a fixed high pressure load of the left ventricle and if this effect could be attributed to normalization of contractile protein phenotype and cardiac collagen content.

2 Rats with constriction of the ascending aorta were treated with the ACE inhibitor quinapril (6 mg kg^{-1} day^{-1}) ($n=95$) or placebo ($n=96$) (starting 6 weeks post surgery.

3 Quinapril treatment improved survival markedly ($P<0.0000001$) during the 24 weeks observation period. There were 69 deaths with placebo and only 25 deaths with quinapril. At the end of the observation period signs of left ventricular backward failure were, however, detected in 75 rats with placebo and in 67 rats treated with quinapril ($P=0.229$). Cox proportional hazard model with time-dependent covariates was used to document that the effect of quinapril treatment had been dependent on time. Quinapril had no significant effect on the development of morphological signs of left ventricular dysfunction after the first 54 days of treatment.

4 The increased isomysin V_3 proportion of hypertrophied non-failing hearts was also not affected by quinapril treatment. Irrespective of treatment, failing hypertrophied hearts were characterized by an increase in left ventricular volume ($P<0.05$), percentage of the 'foetal' isomyosin V_3 ($P<0.05$), and hydroxyproline concentration ($P<0.05$).

5 While the cause of the improved survival remains unknown, quinapril did apparently not interfere with the restitution of 'foetal' gene expression of pressure overloaded cardiomyocytes leading to depressed myocardial performance, ventricular dysfunction and the consecutive myocardial fibrosis.

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Abbreviations: ACE, angiotensin converting enzyme; ANOVA, analysis of variance; HF, heart failure; MHC, myosin heavy chains

Introduction

Angiotensin converting enzyme (ACE) inhibitors improve survival in rats with myocardial infarction (Wollert *et al*., 1994; Nguyen *et al*., 1998). It remains, however, unknown whether the beneficial effects arise solely from unloading of the infarcted left ventricle or from a possibly improved ventricular function which occurs independently of the unloading. To dissociate between these factors, rats with ascending aortic banding have been examined. The ascending aortic banding results in a fixed increased afterload. Thus, any effect of ACE inhibition on cardiac morphology and function could be taken as evidence for a load independent action (Kromer & Riegger, 1988; Weinberg *et al*., 1994; Litwin *et al*., 1995). ACE inhibitors appear to improve the survival of rats with ascending aortic constriction despite the persistent pressure overload on the left ventricle (Weinberg *et al*., 1994; Bruckschlegel *et al*., 1995). This favourable effect could be explained by the hypertrophy regression and improved systolic and diastolic function due to inhibition of an intracardiac renin-angiotensin system (Lonn *et al*., 1994) as well as the ameliorated endothelial function, coronary perfusion and myocardial metabolism arising from elevated kinins (Linz *et al*., 1995).

Since cardiac hypertrophy is correlated with the incidence of heart failure (Levy *et al*., 1990), the hypertrophy regression may appear as a desirable goal of preventive treatments. This notion would be acceptable if the hypertrophy regression results from ventricular unloading. However, concerns arise if a regression occurs but the haemodynamic overload persists. Because concentric hypertrophy normalizes an increased systolic wall stress, it is generally assumed that the hypertrophy is required for long-term compensation of pressure overload (Grossman, 1990; Koide *et al*., 1997). If the hypertrophy is inadequate for normalizing an increased systolic wall stress, afterload mismatch develops accelerating development of heart failure (Ross, 1985). The question is, therefore, addressed in this study whether ACE inhibition without overload reduction delays or prevents the transition from compensatory hypertrophy to heart failure and death.

It has not been assessed experimentally whether and how ACE inhibition affects the transition to heart failure under the condition of a persistent haemodynamic overload (Litwin *et al*., 1995; Weinberg *et al*., 1994). The study of Linz *et al*. (1997) showed that heart failure development can be prevented by ACE inhibition only when both

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overload and hypertrophy are reduced. However, it may be argued that failure of the low non-antihypertensive dose of an ACE inhibitor ramipril to prevent heart failure development may be caused by the insufficient ACE inhibition.

The transition from compensated to failing cardiac hypertrophy has been attributed to a reversion to a 'foetal' pattern of cardiomyocyte gene expression (Swynghedauw, 1999) and adverse remodelling of the ventricular connective tissue matrix (Weber & Brilla, 1991). Therefore, we also tested whether ACE inhibitor quinapril has any long-term effect on foetal gene expression and extracellular matrix remodelling in pressure overloaded myocardium. To monitor phenotypic changes of the cardiomyocyte, myosin isozymes were assessed at the protein level. The isoform switch in myosin heavy chain (MHC) expression can be considered a hallmark of phenotype alterations in overloaded rat heart. β-MHC mRNA begins to accumulate with the onset of overload-induced hypertrophy and the proportion of V_3 isomyosin progressively increases as long as the overload persists, and eventually heart failure develops (Izumo *et al*., 1987; Feldman *et al*., 1993). Furthermore, the hydroxyproline concentration was assessed for monitoring interstitial or perivascular collagen deposition which is diagnostic of an adverse remodelling of the extracellular matrix. Although not all features of myocardial fibrosis are assessed by hydroxyproline concentration, this parameter is generally considered as a useful marker of collagen accumulation (Pickering & Boughner, 1990).

Methods

Animals and treatment

Male 3-week-old Wistar/WU rats were purchased from Charles-River (Kissleg, Germany) and were housed at 21–23°C on a 12 : 12-h light-dark cycle. Rats had free access to tap water and regular chow (Ssniff of Plange, Soest, Germany). Handling of animals and experimental procedures were in accordance with the Institutional Guidelines of the University of Tübingen (Tübingen, Germany).

A gradual increase in pressure overload of the left ventricle was induced by constriction of the ascending aorta in 4–5-week-old rats (Kromer & Riegger, 1988; Litwin *et al*., 1995; Turcani & Rupp, 1997). The ascending aorta was banded with a 3-0 silk suture ligature tied against a 0.8 mm blunt steel wire at a body weight of 90–100 g under Hypnorm® (fluanisone/fentanyl-dihydrogencitrate) anaesthesia (1 ml kg^{-1}, i.p.). The wire was removed, whereby the aorta was constricted to 60–70% of the original diameter. Aged-matched control animals underwent a right thoracotomy and the ascending aorta was isolated but not constricted. After 6 weeks, when the left ventricular aortic pressure gradient was about 90 mmHg and concentric hypertrophy of the left ventricle had developed (Turcani & Rupp, 1997) rats were randomly assigned to a 24-week treatment with quinapril-HCl (6 mg kg^{-1} day^{-1}) or placebo. Quinapril provided by Gödecke AG & Parke-Davis Co (Freiburg, Germany) was given in the drinking water. The dose was maintained by monitoring the daily water consumption and body weight. The dose of 6 mg quinapril kg^{-1} day^{-1} p.o. was chosen since it is known to reduce serum ACE activity to nearly zero in 24 h and to induce regression of left ventricular hypertrophy in rats with ascending aortic constriction (Kromer & Riegger, 1988).

Assessment of heart failure

A post-mortem examination was performed either on the day of death or after the 24 weeks treatment period (under Hypnorm® anaesthesia). Animals were inspected for pleural effusions when heart and lungs were excised. The atria were first trimmed and separated from major vessels. The right ventricular free wall was dissected along the septum. The left ventricle plus septum, right ventricular free wall, atria, and lungs were blotted and weighed. Lung weight was used to assess whether the rats had a failing left ventricle (Afzal & Dhalla, 1992; Pérez *et al*., 1999). K-means cluster analysis (Statistica for Windows, version 5.0, StatSoft, Inc., Tulsa, OK, U.S.A.) was utilized to separate the rats into two groups with different lung weights. During the k-means clustering rats are moved between clusters with the goal to minimize variability within clusters and to maximize variability between clusters. Rats in the group with larger lungs were considered to have a failing left ventricle.

In rats that survived the 24-week treatment period, left ventricular chamber volume was determined prior to autopsy (Hepp *et al*., 1974). Briefly, the atrioventricular groove was ligated with a silk string and the right ventricle was emptied by incision. The left ventricle was filled with a defined volume of saline and emptied in 50 μl steps while recording the passive left ventricular pressure. Three reproducible pressure-volume curves were generated within 3–4 min after the ligation. No effects of anoxia on the pressure-volume relation could be detected within this period of time.

Biochemical parameters

For determination of myosin isozymes of the same cardiac region by non-dissociating polyacrylamide gel electrophoresis in the presence of pyrophosphate (Rupp *et al*., 1992), a portion of the left ventricular free wall (about 100 mg) was cut from the apex to the base and stored in liquid nitrogen. The myosin isozymes were stained with Coomassie brilliant blue R250 and the gels were scanned using a Quick Scan densitometer (Helena Laboratories, Beaumont, TX, U.S.A.). The isozymes V1, V2, V3 were quantitated by measuring peak heights.

Collagen content of ventricular tissue was assessed by determining the hydroxyproline concentration. A 70–100 mg portion of the left ventricular free wall was cut from the apex to the base, freeze-dried and processed essentially as described by Stegemann & Stalder (1967).

Statistical analysis

Statistical evaluations were performed with Statistica for Windows, version 5.0 (StatSoft, Inc., Tulsa, OK, U.S.A.). Multiple comparisons of morphological and biochemical data were made by the analysis of variance and Tukey HSD post-hoc test for unequal sample sizes (Spjotvoll & Stoline-test). Survival in quinapril and placebo treated rats was analysed using the Kaplan-Meier method. According to this method the survivorship function is estimated: $S(t)=\pi[(n-j)/(n-j+1)^{\delta(j)}]$, where $S(t)$ is the estimated survival function, n is the total number of cases, and π denotes the multiplication (geometric sum) across all cases less than or equal to t; $\delta(j)$ is a constant that is either 1 if the j'th case is uncensored (complete) or 0 if it is censored (incomplete, i.e. observations on survival which contain only partial information). Significance of differences in survival between quinapril and placebo treated rats was tested by the Cox F-test. First, a score is assigned to each survival time

and next a Chi-square value is computed based on the sums (for each group) of this score. Frequencies of primary endpoint (death) and secondary endpoint (heart failure) in quinapril and placebo treated group were analysed for differences by Pearson Chi-square test. Cox proportional hazard model with time-dependent covariates was used to assess the time dependence of effects of the quinapril treatment. Statistical significance was accepted at the level of $P<0.05$.

Results

After constriction of the aorta in 220 rats, five rats died within 2 h post surgery and 12 rats died before treatment with quinapril started. When 12 randomly selected rats with ascending aortic constriction and 12 sham-operated rats were compared after an initial 6-weeks pressure overload, signs of left ventricular hypertrophy with a concentric configuration were observed. Left ventricular weight was increased (rats with ascending aortic constriction vs sham operated rats; 985 ± 97 vs 644 ± 30 mg, $P<0.05$) while both, left ventricular chamber volume (322 ± 32 vs 374 ± 23 mm^3, $P<0.05$) and ratio of left ventricular chamber volume-to-wall mass (0.33 ± 0.04 vs 0.58 ± 0.04, $P<0.05$) were decreased. In rats with aortic constriction, the proportion of isomysosin V_3 (23 ± 3 vs $13\pm2\%$, $P<0.05$) was increased while the hydroxyproline content remained unchanged (2.75 ± 0.35 vs 2.67 ± 0.22 mg g^{-1} dry weight). No signs of pulmonary congestion were observed.

Six weeks after surgery, 95 rats out of the remaining 191 rats with left ventricular pressure overload, were randomised to quinapril treatment and 96 rats remained without treatment. Administration of quinapril improved ($P<0.000001$) survival in rats with ascending aortic constriction (Figure 1). Twenty-five per cent of placebo-treated rats with aortic constriction died within the first 23 days. In contrast, quinapril prolonged the 25th percentile of the survivorship function to 161 days. Thus, the benefit of treatment was seen soon after randomisation and persisted throughout the trial. The median survival of placebo-treated rats was 117 days and remained undefined in quinapril treated rats, i.e. was greater than the 168 day observation period. None of the rats in the sham-operated group died.

Dead rats and rats that survived the 24 weeks treatment period were examined for macroscopic signs of left ventricular insufficiency. Based on the finding that the lungs are enlarged with long-standing left ventricular insufficiency (Braunwald & Grossman, 1992), we used the k-means clustering to define two groups of rats with significantly different lung weights (Figure 2). Rats in the cluster with larger lung weights were considered to have a chronically failing left ventricle. There was no overlap between these two clusters and all lung weights in the failing cluster were higher than 2.4 g. The largest lung weight in the non-failing cluster was 1.88 g. No significant differences in lung weights were detected between quinapril-treated and untreated succumbed rats or rats that belonged to the failing group (Figure 3). Lung weights in sham operated rats and non-failing rats with aortic constriction were not different.

Significantly increased atrial and right ventricular weights as further morphological signs of chronic blood stasis, elevated

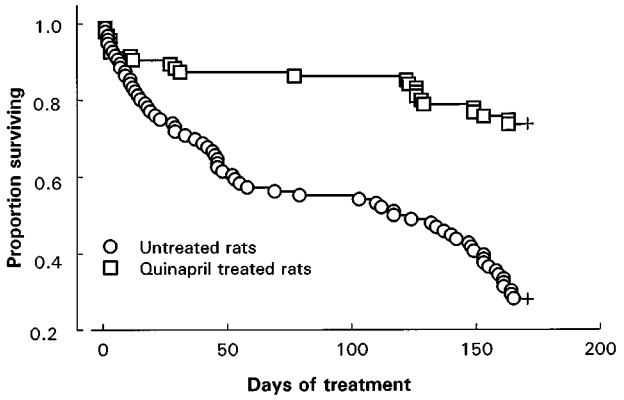

Figure 1 Kaplan-Meier survival curves for rats with ascending aortic constriction. Number of untreated rats with ascending aortic constriction: 96; number of quinapril (6 mg kg^{-1} day^{-1}) treated rats with ascending aortic constriction: 95. The survival in both groups was significantly different by Cox's *F*-test ($P<0.000001$). Crosses mark censored (incomplete) observations.

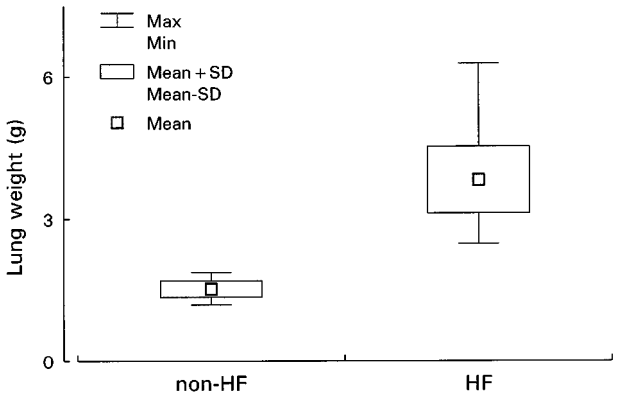

Figure 2 Result of the k-means clustering that define two groups of rats with significantly different lung weights. Rats in the cluster with larger lung weights were considered to have chronically failing left ventricle (HF); non-HF, rats without signs of left ventricular backward failure. Max, maximal value in the cluster; min, minimal value in the cluster; SD, standard deviation. Number of rats in the non-HF-group: 63, HF-group: 142.

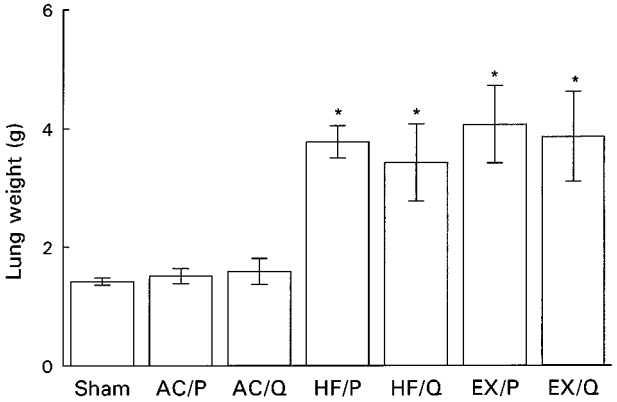

Figure 3 Bar graph showing lung weight: in rats with ascending aortic constriction that died before the end of observation period and were treated with placebo (EX/P) or quinapril (EX/Q); in rats with ascending aortic constriction considered to have failing left ventricle and were treated with placebo (HF/P) or quinapril (HF/Q); in rats with ascending aortic constriction that survived the observation period without signs of left ventricular backward failure and were treated with placebo (AC/P) or quinapril (AC/Q); in sham operated rats treated with placebo (Sham). *Significantly ($P<0.05$) different from Sham by ANOVA and Tukey HSD *post-hoc* test for unequal sample sizes. Whiskers determine standard deviation. Number of rats in the Sham-group: 14, AC/P-group: 21, AC/Q-group: 28, HF/P-group: 6, HF/Q-group: 42, EX/P-group: 69, EX/Q-group: 25.

Table 1 Body weight and cardiac morphometry in sham operated rats and rats with ascending aortic constriction at the time of autopsy

	Sham		*Aortic constriction*				
Treatment	placebo	placebo	quinapril	placebo	quinapril	placebo	quinapril
Status at the end of observation period	non-HF	non-HF	non-HF	HF	HF	died	died
Number of rats at the end of observation period	14	21	28	6	42	69	25
Age of rats at the time of autopsy (weeks)	36	36	36	36	36	3-36	7-30
Body weight (g)	428±19	436±27	389±37	384±43	351±53*	309±76*†	263±61*‡
Left ventricular weight (mg)	889±58	1220±62*	1158±103*	1295±122*	1185±92*	1162±154*	1068±113*
Left ventricular weight/body weight (mg g^{-1})	2.08±0.13	2.81±0.16*	3.02±0.5*	3.43±0.65*	3.42±0.39*	3.91±0.68*†	4.23±0.92*‡
Left ventricular weight/tibia length (mg mm^{-1})	21.3±1.2	28.9±1.2*	27.8±2.8*	31.5±3.6*	29.3±2.0*	29.7±3.4*	28.1±2.2*
Right ventricular weight (mg)	216±19	241±24	214±21	436±50*†	460±80*‡	423±85*†	378±56*‡
Right ventricular weight/body weight (mg g^{-1})	0.51±0.04	0.55±0.06	0.55±0.06	1.15±0.21*†	1.33±0.27*‡	1.46±0.47*†	1.51±0.42*‡
Atrial weight (mg)	97±19	141±36	105±9	327±48*†	302±41*‡	332±86*†	301±70*‡

HF indicates rats with signs of heart failure; non-HF, rats without signs of heart failure. Values are means±s.d. Data were analysed by ANOVA and Tukey HSD post hoc test for unequal sample sizes. Statistical significance was accepted at the level of $P<0.05$. *Significantly different from sham-operated rats; †significantly different from non-HF placebo treated rats with aortic constriction; ‡significantly different from non-HF quinapril treated rats with aortic constriction.

Table 2 Effect of quinapril on heart failure with and without death in rats with ascending aortic constriction

	Total number of rats in the group	*Rats with morphological signs of left ventricular failure*		
		Total	*Died*	*Survived*
Aortic constriction/placebo	96	75	69	6
Aortic constriction/quinapril	95	67	25	42
P-value		0.2293	0.000001	0.000001

Data were analysed for differences between quinapril and placebo treated group by Pearson Chi-square test.

blood pressures in the pulmonary circulation, and augmented left ventricular filling pressures were detected in all rats with high lung weights (Table 1). When the effect of ACE inhibition on frequencies of morphological signs of left ventricular backward failure was assessed, no significant improvement was observed (Table 2). An analysis based on Cox proportional hazard model with time-dependent covariates showed that quinapril treatment had diminished ($P<0.0004$) the development of morphological signs of left ventricular dysfunction only during the first 53 days of treatment (Figure 4a) but not later (Figure 4b).

In animals that survived the observation period, left ventricular geometry, isomyosin composition and hydroxyproline concentration were assessed. Dilation of the left ventricle was observed in rats with the macroscopic evidence of left ventricular backward failure. Left ventricular chamber volume and the ratio of left ventricular chamber volume-to-wall mass was increased as compared with non-failing rats with aortic constriction (Table 3). Rats with hypertrophied left ventricles exhibited an increased proportion of myosin V_3 and a correspondingly reduced proportion of V_1, while myosin V_2 was not altered (Table 3). Quinapril treatment did not modify the distribution of myosin isozymes either in failing nor in non-failing pressure overload ventricles. Hydroxyproline was not significantly altered in rats with pressure overloaded non-failing left ventricles (Table 3). In rats with pulmonary congestion, the proportion of V_3 was increased further (Table 3) although ventricular weight remained unchanged when referred to tibia length which represents a marker of general body growth (Table 1). Also hydroxyproline concentration was moderately increased (Table 3) and was correlated ($P<0.001$) with the proportion of myosin V_3 (Figure 5). However, a significant correlation could not be demonstrated in the subgroups of sham-operated rats and rats with aortic constriction without pulmonary congestion (Figure 5). The quinapril treatment neither prevented cardiac failure nor the increase in myosin V_3 or hydroxyproline concentration.

Discussion

With respect to overall mortality, we confirmed that treatment with ACE inhibitors improved survival in rats with ascending aortic constriction (Weinberg *et al.*, 1994; Bruckschlegel *et al.*, 1995). By contrast, the frequencies of morphological signs of left ventricular backward failure throughout the observation period were not significantly altered by the ACE inhibition. All dead rats exhibited morphological signs of left ventricular failure as well as 22% of survived untreated animals and 60% of survived quinapril treated rats. If dead rats and those that survived were evaluated together, the quinapril treatment did not affect the appearance of morphological signs of left ventricular failure during the whole treatment period. However, the effect of quinapril on heart failure development was time-dependent. When only the first 53 days of treatment were considered, the risk associated with the heart failure was significantly lower in the quinapril treated group. On the contrary, the incidence of heart failure was not significantly different in the later period of 54 to 168 days of treatment.

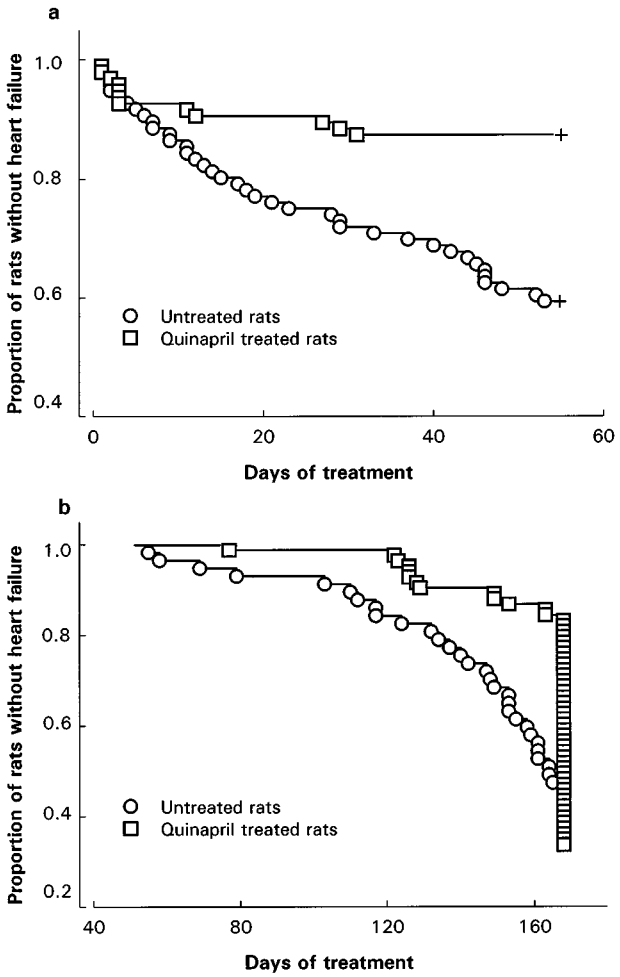

Figure 4 Kaplan-Meier survival curves for rats with ascending aortic constriction. Terminal event was not death but presence of morphological signs of left ventricular dysfunction assessed either in succumbed rats or euthanized rats that survived the treatment period. (a) First 53 days of treatment. Number of untreated rats with ascending aortic constriction: 96, uncensored: 39, censored: 57. Number of quinapril treated rats with ascending aortic constriction: 95, uncensored: 12, censored: 83. The frequencies of morphological signs of left ventricular dysfunction in both groups were significantly different by Cox's *F*-test ($P<0.00036$). Crosses mark censored (incomplete) observations. (b) Period of 54–168 days of treatment. Number of untreated rats with ascending aortic constriction: 57, uncensored: 36, censored: 21. Number of quinapril treated rats with ascending aortic constriction: 83, uncensored: 55, censored: 28. The frequencies of morphological signs of left ventricular dysfunction in both groups were not significantly different by Cox's *F*-test ($P=0.154$).

In the present study, the development of left ventricular failure was associated with enlargement of left ventricular chamber volume, increase in left ventricular chamber volume-to-wall mass ratio, i.e. dilation, a further increase of β-MHC expression and myocardial fibrosis. While the proportion of isomyosin V_3 was increased in all hypertrophied ventricles, the hydroxyproline content was raised only in failing ventricles. This could be a consequence of a neurohumoral response to the peripheral hypoperfusion (Brilla *et al.*, 1995). Thus, the shift in the isomyosin synthesis preceded the development of myocardial fibrosis. Assuming that the hypertrophy compensates adequately for the increased wall stress, the question remains why progression to heart failure occurred. The myosin V_3 proportion and thus β-MHC expression was increased during the period preceding the occurrence of heart failure and was associated with depressed values of rate of contraction and relaxation (Turcani & Rupp, 1997). The progressively augmented expression of 'foetal' genes, as monitored by a marked increase in β-MHC expression, could thus be responsible for the further depression of contractile function. As a compensatory response to the decreased contractility, a transition from cardiomyocyte thickening to cardiomyocyte

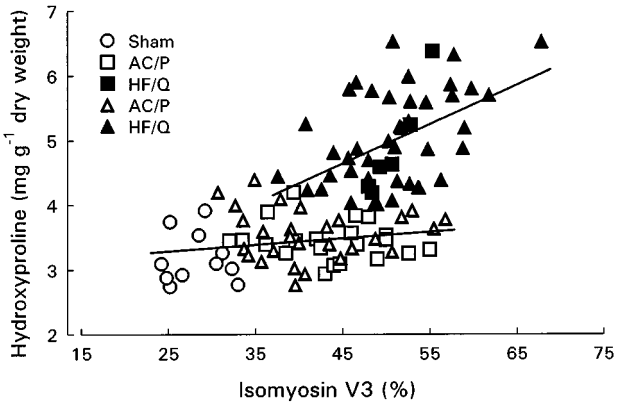

Figure 5 Correlation between the proportion of myosin V_3 and myocardial hydroxyproline concentration in sham-operated rats and rats with constriction of the ascending aorta. HF, heart failure; AC, aortic constriction; p, placebo; Q, quinapril. The bottom correlation involved sham-operated rats and rats with ascending aortic constriction without heart failure: $y=3.04+0.01x$, $r=0.229$, $P>0.05$. The top correlation involved rats with signs of left ventricular insufficiency: $y=1.898+061x$, $r=0.488$, $P=0.0004$.

Table 3 Left ventricular chamber volume, myosin isozymes population, and hydroxyproline concentration in rats surviving observation period

	Sham		*Aortic constriction*		
Treatment	placebo	placebo	quinapril	placebo	quinapril
Status at the end of observation period	non-HF	non-HF	non-HF	HF	HF
Number of rats at the end of observation period	14	21	28	6	42
Left ventricular chamber volume (mm^3)	440±47	342±35*	324±43*	455±26†	443±53‡
Left ventricular chamber volume/weight ($mm^3\ mg^{-1}$)	0.50±0.07	0.28±0.03*	0.28±0.04*	0.35±0.03*†	0.38±0.06*‡
Myosin V_1 (%)	44±4	27±6*	29±7*	17±3*†	17±5*‡
Myosin V_2 (%)	29±1	30±1	29±2	32±2	32±3*‡
Myosin V_3 (%)	27±3	44±6*	42±7*	51±3*	51±6*‡
Hydroxyproline (mg g^{-1} dry weight)	3.15±0.35	3.45±0.30	3.56±0.39	4.89±0.82*†	5.04±0.73*

Left ventricular chamber volume is given for the intraventricular pressure 6 mmHg. HF indicates rats with signs of heart failure; non-HF, rats without signs of heart failure. Values are means±s.d. Data were analysed by ANOVA and Tukey HSD *post hoc* test for unequal sample sizes. Statistical significance was accepted at the level of $P<0.05$. *Significantly different from sham-operated rats; †significantly different from non-HF placebo treated rats with aortic constriction; ‡significantly different from non-HF quinapril treated rats with aortic constriction.

elongation and so dilative ventricular remodelling could be initiated.

In animals with various forms of cardiac pressure or volume overload, ACE inhibitors reduced detrimental remodelling of cardiomyocytes and myocardial extracellular matrix, ameliorated ventricular systolic and diastolic function, induced cardiac hypertrophy regression and improved survival (Juggi *et al*., 1993; Brilla *et al*., 1996; Linz *et al*., 1997). However, in most of these experiments the benefit caused by ACE inhibition was associated with an unloading of the heart and was, therefore, predictable. The present study demonstrates that ACE inhibition improved survival in rats with a fixed left ventricular overload. Although the cardiac geometry and molecular structures were assessed only at the end of study, it appears likely that in the preceding periods the quinapril treatment had slowed the increase in myosin V_3 proportion of hypertrophied hearts or fibrosis of failing hearts and consequently the development and progression of the failing heart syndrome. However, quinapril had failed to prevent transformation of crucial determinants of an impaired ventricular performance when left ventricular systolic pressure remained elevated. Previous studies which failed to observe the heart failure development and associated detrimental changes in ventricular geometry, cardiomyocyte gene expression and extracellular matrix composition were probably too short for detecting this fatal outcome.

In conclusion, the ACE inhibition did not prevent the development of morphological signs of left ventricular backward failure. However, the evolution of left ventricular dysfunction to the level which did not permit survival was slowed by the ACE inhibition. Since the occurrence of the 'foetal' phenotype and the dilative remodelling of the left ventricle was not prevented, it is proposed that the expression of the 'foetal' phenotype as monitored by myosin isozymes contributes to the transition from compensated to failing cardiac hypertrophy also in the case of quinapril treated rats.

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