Molecular and Cellular Biochemistry **147:** 89–97, 1995.

Angiotensin converting enzyme inhibitors, left ventricular hypertrophy and fibrosis

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Abstract

From pharmacological investigations and clinical studies, it is known that angiotensin converting enzyme (ACE) inhibitors exhibit additional local actions, which are not related to hemodynamic changes and which cannot be explained only by interference with the renin angiotensin system (RAS) by means of an inhibition of angiotensin II (ANG II) formation. Since ACE is identical to kininase II, which inactivates the nonapeptide bradykinin (BK) and related kinins, potentiation of kinins might be responsible for these additional effects of ACE inhibitors.

a) In rats made hypertensive by aortic banding, the effect of ramipril in left ventricular hypertrophy (LVH) was investigated. Ramipril in the antihypertensive dose of 1 mg/kg/day for 6 weeks prevented the increase in blood pressure and the development of LVH. The low dose of ramipril (10 μg/kg/day for 6 weeks) had no effect on the increase in blood pressure or on plasma ACE activity but also prevented LVH after aortic banding. The antihypertrophic effect of the higher and lower doses of ramipril, as well as the antihypertensive action of the higher dose of ramipril, was abolished by coadministration of the kinin receptor antagonist icatibant. In the regression study the antihypertrophic actions of ramipril were not blocked by the kinin receptor antagonist. Chronic administration of BK had similar beneficial effects in a prevention study which were abolished by icatibant and N^G-nitro-L-arginine (L-NNA).

In a one year study the high and low dose of ramipril prevented LVH and fibrosis. Ramipril had an early direct effect in hypertensive rats on the mRNA expression for myocardial collagen I and III, unrelated to its blood pressure lowering effect.

b) In spontaneously hypertensive rats (SHR) the preventive effects of chronic treatment with ramipril on myocardial LVH was investigated. SHR were treated in utero and, subsequently, up to 20 weeks of age with a high dose (1 mg/kg/day) or with a low dose (10 μg/kg/day) of ramipril. Animals on a high dose remained normotensive, whereas those on a low dose developed hypertension in parallel to vehicle-treated controls. Left ventricular mass was reduced only in high-dose-treated, but not in low-dose treated animals but both groups revealed an increase in myocardial capillary length density. In SHR stroke prone animals cardiac function and metabolism was improved by ramipril and abolished by coadministration of icatibant.

In contrast to the prevention studies, in a regression study ramipril reduced cardiac hypertrophy also by low dose treatment.

c) In rats chronic nitric oxide (NO) inhibition by N^G-nitro-L-arginine-methyl ester (L-NAME) treatment induced hypertension and LVH. Ramipril protected against blood pressure increase and partially against myocardial hypertrophy.

These experimental findings in different models of LVH characterise ACE inhibitors as remarkable antihypertrophic and antifibrotic substances. (Mol Cell Biochem **147:** 89–97, 1995)

Key words: left ventricular hypertrophy, fibrosis, ramipril, autocrine-paracrine actions, ACE inhibitors, bradykinin, prostacyclin

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Introduction

Left ventricular hypertrophy (LVH) is regarded – beside high blood pressure as an independent risk factor for cardiovascular diseases especially with respect to the sequels of ischemia, arrhythmias and left ventricular dysfunction [1].

The renin angiotensin system (RAS) has been implicated in the development and maintenance of hypertension and cardiac hypertrophy [2]. Angiotensin converting enzyme (ACE) inhibitors may partly suppress the cardiac hypertrophic response by reducing the formation of angiotensin II (ANG II), which stimulates hypertrophy, matrix protein and collagen synthesis [3, 4].

From new insights into the molecular biology of the RAS we know that ANG II is not only synthesised in the blood stream but also locally in tissues [5–11]. Thus, the traditional endocrine concept has evolved into a concept of autocrine-paracrine functions of the RAS [12]. Consequently ACE inhibitors may exert part of their pharmacological effects via these autocrine-paracrine mechanisms including not only the RAS but also the kallikrein-kinin-system [13, 14].

ACE inhibitors attenuate the formation of ANG II and accumulate kinins by inhibition of their degradation, namely bradykinin (BK). Thereby, they prevent the systemic and local actions of ANG II and potentiate the local and/or cardiovascular and metabolic effects of BK [15, 16]. Especially the effects of kinins had been underestimated for long time.

ACE inhibitors seem to have a more pronounced antihypertrophic effect pointing to the importance of interference with the RAS and the kallikrein kinin system to prevent or regress this target organ damage [17].

Antihypertrophic effect of ACE inhibitors in rats with aortic constriction and pressor overload hypertrophy

In our studies renal hypertensive rats with LVH following aortic constriction between the origin of renal arteries were used. After aortic banding during development of pressure overload hypertrophy the circulating RAS is markedly activated. However, once LVH is established at 6 weeks following aortic constriction, plasma values of renin activity and aldosterone are in the range of sham operated animals. Immediately after aortic banding ACE activity and ACE mRNA levels within the myocardium as well as intracardiac ANG I to ANG II conversion rates were increased [18, 19].

In rats subjected to abdominal aortic constriction and LVH an increase in vulnerability to arrhythmias was found [20]. This is in line with observations in patients with LVH [21].

To investigate the possible involvement of locally formed ANG II by the cardiac RAS and its possible trophic properties [22, 23], long-term administration of an ACE inhibitor was compared with other antihypertensive agents in the prevention and regression of LVH [24]. The effects of equipotent oral antihypertensive doses of the ACE inhibitor ramipril (1 mg/kg/day), the calcium antagonist nifedipine (30 mg/kg/day), and the arterial vasodilator dihydralazine (30 mg/kg/day) on cardiac mass in rats subjected to constriction of the abdominal aorta were compared. Daily oral treatment over 6 weeks was started immediately following acute aortic constriction (prevention experiments) or 6 weeks after aortic banding, when hypertension and cardiac hypertrophy were established (regression experiments). Groups of sham operated animals and untreated animals with aortic banding served as controls. In the regression experiments an additional group received ramipril in a low dose of 10 μg/kg/day.

All three drugs lowered the blood pressure to a similar level with the exception of the low dose of ramipril, which was without effect on high blood pressure. Only the ACE inhibitor induced a significant and complete prevention or regression of cardiac hypertrophy compared to control normotensive rats which were similar to the sham-operated normotensive rats. Surprisingly the low dose of ramipril showed the same complete regression of cardiac hypertrophy as seen with the antihypertensive dose of the ACE inhibitor [24].

A comparable antihypertrophic effect was observed in a recent one year study in rats [25]. The aim of this study was to separate local cardiac effects using a low dose from those effects on systemic blood pressure when using an antihypertensive dose of ramipril. After one year, treatment with both doses the antihypertensive and the low dose which had no effect on blood pressure had prevented LVH. Plasma ACE activity was inhibited in the high but not in the low dose group, whereas the conversion of ANG I–ANG II in isolated aortic segments was suppressed in both treated groups. Plasma catecholamines were increased in the vehicle control group but treatment with either dose of the ACE inhibitor normalised the values. The myocardial phosphocreatine/ATP ratio as an indicator for the energy state of the heart was reduced in the vehicle control group, whereas the hearts from treated animals showed a normal ratio comparable to hearts from sham operated animals.

After one year from each group 7 animals were separated, treatment stopped and housed for additional 6 month (withdrawal experiments). Withdrawal of the treatment did not change left ventricular weight to body ratio in the different groups and in the earlier group with high ACE inhibitor treatment blood pressure did not reach the value of the stenosis vehicle group.

These experiments showed that long-term treatment with an ACE inhibitor effectively prevented cardiac hypertrophy even in the presence of high blood pressure. This protective effect was still present after 6 month treatment, withdrawal. Local ACE inhibition involving decreased ANG II formation, an increased kinin accumulation and an attenuation of sym-

pathetic activities should be considered as factors evoking these long term beneficial cardiac effects of ACE inhibitors.

The dissociation between the effects of ramipril on blood pressure in a high dose and on cardiac mass already in a low dose stresses the role of factors other than blood pressure and afterload in the development of hypertensive cardiac hypertrophy.

From other series of experiments using the same model it was known however, that losartan was more active to regress an already established LVH than to prevent the development of cardiac hypertrophy [26, 27]. Therefore during the development of LVH other factors than ANG II seem to play a role. Since inhibition of ACE besides reducing ANG II formation also increases kinin levels, kinins might contribute via generation of nitric oxide (NO) and prostacyclin (PGI_2) to the prevention of the hypertrophic response.

Patients (n:115) with essential hypertension and LVH [28], after a selection period of 4–6 weeks under antihypertensive therapy with 20 mg furosemide daily, were randomized in a double blind manner to receive either placebo, the subhypotensive dose of 1.25 mg or the antihypertensive dose of 5 mg ramipril daily for 6 months. Treatment with furosemide was continued during this period. Ramipril at both treatment regimens for 6 months induced LVH regression, independent of changes in ambulatory blood pressure in patients under antihypertensive therapy.

Contribution of kinins to the antihypertrophic effect of ramipril

To evaluate the role of BK and related kinins in the antihypertrophic effect of ACE inhibitors the influence of the kinin receptor antagonist icatibant on the effects of ramipril on LVH in rats with aortic banding was investigated [29]. Ramipril in the antihypertensive dose of 1 mg/kg per day p.o. for 6 weeks prevented the increase in blood pressure and the development of LVH. Plasma ACE activity was significantly inhibited. The low dose of ramipril (10 μg/kg/day p.o. for 6 weeks) had no effect on the increase in blood pressure and on plasma ACE activity but also prevented LVH after aortic banding. The antihypertrophic effect of the high and the low dose ramipril as well as the antihypertensive action of the high dose of ramipril were abolished by icatibant. However, when treatment (high and low) was started 6 weeks after aortic constriction (regression experiments) the kinin receptor antagonist was not able to reverse the antihypertrophic effects of the ACE inhibitor.

Furthermore, chronic administration of BK in a dose without effect on blood pressure via osmotic minipumps prevented development of LVH, however did not induce regression of LVH. The preventive effect of BK was abolished by coadministration of icatibant or of the NO synthase inhibitor L-NNA [30].

These data suggest that kinins are involved in the antihypertrophic effects of ACE inhibitors in the developmental phase of LVH in rats with aortic constriction. NO releasing vasodilators and cyclic GMP are known to be antimitogenic and antiproliferative, *in vitro* [31, 32]. Similar effects were found for PGI_2 and cyclic AMP [33]. Both NO and PGI_2 when increased by kinin accumulation following ACE inhibition may contribute to these antihypertrophic effects of ACE inhibitors [34].

From these experimental studies in rats with pressure overload LVH one can assume that kinin accumulation induced by ACE inhibitors may contribute to the antihypertrophic action during the prevention phase, whereas attenuation of ANG II formation by the ACE inhibitor may be more important during the regression period.

Role of ACE inhibition on myocardial fibrosis

ANG II has been demonstrated to act as a growth factor in a variety of tissues including cardiac fibroblasts. Cardiac fibroblasts can mediate ANG II induced cardiac myocyte hypertrophy through a paracrine mechanism stimulating the production of a transferable growth factor or factors in cardiac fibroblasts [35]. ACE inhibition might at least in part via reduced ANG II formation positively interfere with these mitogenic signaling pathways in cardiac fibroblasts.

In line with the values for LVH obtained in the one year study are the observations on the occurrence of myocardial fibrosis which was evaluated by staining the left ventricular tissue for fibronectin. Myocardial fibrosis was not seen in hearts from animals treated with the high as well as the low dose of ramipril, whereas in hearts from vehicle treated rats with aortic banding, myocardial fibrosis occurred.

Myocardial fibrosis did not recur after 6 months withdrawal of ACE inhibitor treatment.

In the same model cardiac mRNA levels of the collagens α_1(I) [col I] and α_1(III) [col III] was isolated from control and aortic banded-hypertensive rats as well as from rats treated with either the high or the low dose ramipril after 2 and 6 weeks aortic constriction. Banded hypertensive rats with vehicle treatment showed increased cardiac col mRNA levels. Low dose ramipril treatment led to normal col mRNA levels but blood pressure was still elevated, whereas high dose ramipril treatment reduced col and blood pressure below control values. At 6 weeks blood pressure and col were at control levels in animals with high dose ramipril treatment. These results indicate that ramipril has a direct and early effect in hypertensive rats on the mRNA expression of col I and col III, unrelated to its blood pressure lowering effect. Influences of transcriptional control of collagen gene expression by ramipril are thus able to reduce an increased left ventricu-

lar weight to body weight ratio and, possibly hypertrophy [36].

Determination of the fibronectin content in ACE inhibitor treated animals showed in the prevention study lower values than in the regression study. Fibrosis was seen until 12 weeks after aortic constriction (regression study).

Beyond 4 weeks of renovascular hypertension, an accumulation of fibrillar collagen is seen within the adventitia of intramyocardial coronary arteries. From their perivascular location fibrillar collagen begins to radiate outward into neighboring intramuscular spaces [37–39]. Eight weeks later, a progressive perivascular and interstitial fibrosis has developed [38, 40]. After 12 weeks, foci replacement fibrosis secondary to myocyte necrosis, appear predominantly within the endomyocardium of the rat [41, 42]. At 20 weeks of renovascular hypertension, the complete pattern of diffuse interstitial and perivascular fibrosis has developed. The reparative fibrosis becomes more pronounced at 32 weeks or more, where overall collagen volume fraction accounts of the myocardial structural space [41] as shown in the one year study.

In our regression study the fibronectin values in both ramipril treated groups (low and high) were comparable to values found in sham operated animals (~ 23%) whereas in banded vehicle treated rats the values ranged about 43%. Cotreatment with icatibant did not abolish this antifibrotic effect of ramipril. These observations would imply that endothelium derived kinins increased by ACE-inhibition in this phase might act more on myocytes than on fibroblasts in this model of renovascular hypertension. Thus, when one considers the presence or absence of the remodeling of the interstitial space, hypertrophy is a heterogenous process and myocyte and nonmyocyte compartments appear to have independent regulatory controls. Local concentrations of stimulators (e.g. ANG II, endothelin, aldosteron, norepinephrine) and inhibitors (e.g. kinins, PGI_2, NO, atrial natriuretic peptide) may regulate fibroblast collagen turnover and the healing response [43].

Effects of ACE inhibitors on cardiac and vascular hypertrophy in Spontaneously Hypertensive Rats (SHR)

Earlier chronic studies in SHR had shown that oral administration of ramipril in doses of 0.1, 1, and 10 mg/kg/day resulted in a dose-dependent antihypertensive effect, with a threshold antihypertensive dose of 0.1 mg/kg/day [44, 45]. Measurements of ACE activity in homogenates of hearts from normotensive rats pretreated with single doses of 1, 10 and 100 μg/kg of ramipril demonstrated a long-lasting inhibition of ACE activity at all doses [46].

SHR and stroke prone SHR (SHRSP), animals with genetic hypertension associated with normal to low plasma renin levels, were treated with different ACE inhibitors at antihypertensive high doses (1 mg/kg per day) and low doses (0.01 mg/kg per day). Prevention studies were begun before hypertension developed (prenatally) and were continued for 20 weeks. The effects of chronic ACE inhibitor treatment on myocardial LV weight and on capillary length density as well as on structural alterations in mesenteric arteries were investigated [47–49].

Early-onset treatment with high doses of the ACE inhibitors ramipril and zabicipril prevented or attenuated the development of hypertension and prevented the development of cardiac LVH. These effects were not altered by chronic kinin receptor blockade with icatibant demonstrating that kinins do not contribute to the antihypertensive and antihypertrophic actions in genetically hypertensive rats.

The development of LVH is associated with a diminished capillary density leading to relative ischemia. Therefore, the effect of chronic ACE inhibitor treatment on cardiac capillary length density was determined. The results revealed an increase in the length of capillaries per volume of the left ventricle in animals treated with an antihypertensive dose (high dose) of the ACE inhibitors indicating an improved oxygen supply of the heart [47, 50].

In addition, high dose treatment with ramipril and zabicipril affected the development of vascular structural alterations. This effect was demonstrated by the decrease in the number of smooth muscle cell layers in the vascular media and the media to lumen and wall to lumen ratios of mesenteric arteries [50, 51].

In contrast to the antihypertensive dose, cardiac hypertrophy as well as vascular structural alterations were not affected by chronic early-onset treatment with low doses of the ACE inhibitors ramipril, zabicipril and perindopril. Therefore, in genetically hypertensive animals the effects of the ACE inhibitors on the development of cardiac and vascular hypertrophy appear to be related to their antihypertensive actions [47–51]. On the other hand, low-dose ACE inhibitor treatment like high-dose treatment improved myocardial capillary length density [48]. This suggests that capillary proliferation is independent of blood pressure and of structural alterations in the myocardium. The underlying mechanism for the ACE inhibitor induced myocardial capillary growth is not known. One possible explanation resides in the kinin potentiating effect of the ACE inhibitor. BK has been shown to improve myocardial blood flow, even at very low concentrations [52]. An enhanced myocardial blood flow on the other hand appears to be the common denominator of all experimental conditions associated with myocardial capillary proliferation [53, 54]. In addition, long term ACE inhibitor treatment of SHRSP improved cardiac function, increased coronary flow and myocardial tissue concentrations of glycogen and the energy-rich phosphates ATP and creatine phosphate as will be outlined below [49]. These effects could be prevented by chronic kinin receptor blockade with icatibant. In addition,

these effects are comparable with the known cardiac metabolic effects of BK to enhance myocardial glucose uptake in normoxic isolated rat hearts [55]. Interestingly, in the aging mouse ACE inhibition was found to decrease renal and myocardial sclerosis and to increase the number of mitochondria in heart and liver cells, which was associated with a significant increase in survival [56]. Further studies comparing specific ANG II and BK receptor antagonists will particularly have to address the possible effect of an ACE inhibitor-induced kinin potentiation on myocardial capillary growth and mitochondrial density in more detail.

The observations, that low-dose ACE inhibitor treatment did not affect the development of LVH in SHR and SHRSP is at variance with the results reported in the coarctation model of renal hypertension mentioned above (Fig. 1). The discrepancy between these studies could be explained by the fact that the coarctation model represents a highly renin-dependent model of experimental hypertension, which may respond to ACE inhibition, more marked than the SHR and SHRSP, models with normal to low plasma renin.

In a regression study adult 16 week old SHR with established hypertension and cardiac and vascular hypertrophy were treated for 16 weeks with the ACE inhibitors ramipril and zabicipril at doses of 1 mg/kg per day and 0.01 mg/kg per day. Treatment with the high dose of both drugs normalized blood pressure and reduced cardiac hypertrophy, but had no effect on morphometric parameters in the mesenteric arteries [47, 50]. Thus, mesenteric vascular hypertrophy could only be prevented by early-onset high-dose treatment with ACE inhibitors but not once hypertrophy has been established. In contrast, cardiac hypertrophy was significantly reduced by low dose treatment with ramipril (Fig. 1), but not with zabicipril. It should be noted that the hypertension-induced increase in vascular mass of SHR mensenteric arteries appear to be mainly due to hyperplasia, that is an increase in the number of cells. On the other hand, the increase in cardiac mass is mainly a result of an increase in cell size (hypertrophy). Most likely, a regression of an increased number of cells is more difficult to achieve any antihypertensive treatment than a regression of an increased cell size.

These results demonstrate, that in SHR early-onset treatment with ramipril can induce myocardial capillary growth, even at doses too low to antagonise the development of hypertension or LVH. This ability of ramipril to induce capillary growth might be of great importance for induction of coronary collateral vessels in humans with coronary artery disease and heart failure [57].

Meanwhile other investigators found similar beneficial

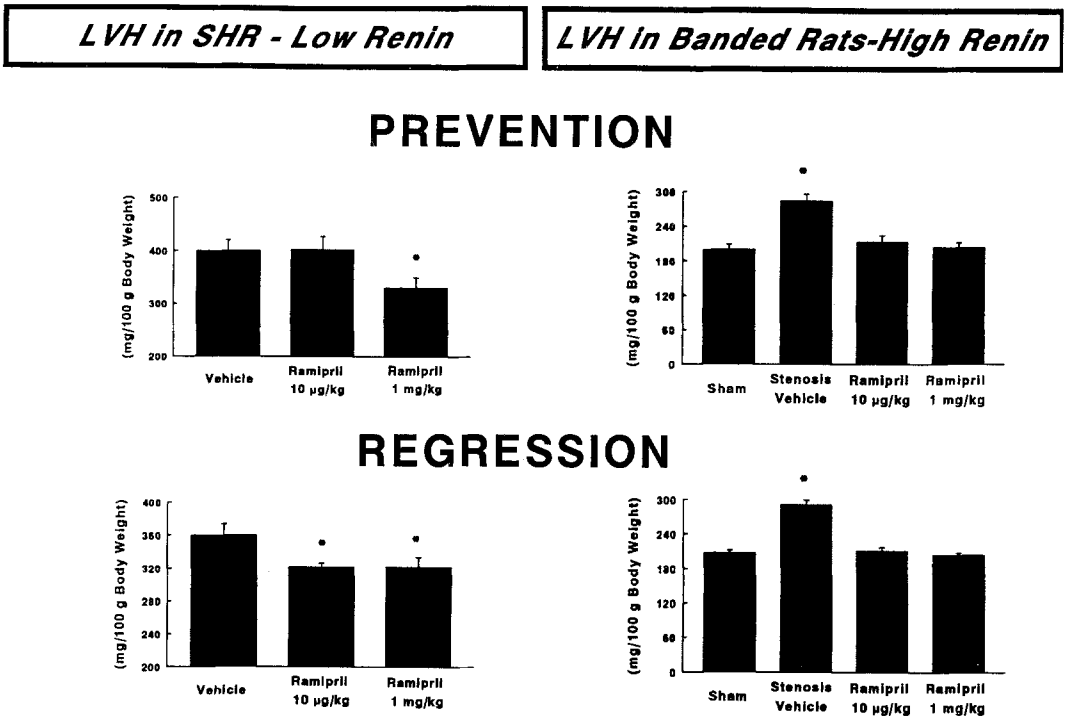

Fig. 1. Effect of long term oral treatment with ramipril, high (1 mg/kg/day) and low (10 µg/kg/day) dose, on left ventricular hypertrophy (LVH) in rats. Left hand side: Spontaneously hypertensive rats (SHR) with low plasma renin levels. In a prevention study rats were treated *in utero* and continued for 20 weeks. In a regression study adult 16 week old SHR with established hypertension and cardiac hypertrophy were treated for 16 weeks with the ACE inhibitor. Right hand side: In a prevention study rats with aortic constriction and high plasma renin levels were treated immediately after operation for 6 weeks. In a regression study treatment started 6 weeks – after aortic constriction after LVH hypertrophy has been established – for 6 weeks. *$p < 0.05$ vs. vehicle and sham respectively.

effects on LVH and/or fibrosis by ACE inhibition without blood pressure reduction [58–61], whereas others could not observe beneficial effects on LVH by low dose ACE inhibitor treatment [62].

Cardiac and vascular function in SHR

Low- and high-dose treatment with ramipril inhibited vascular ACE activity ex vivo demonstrated by the inhibition of aortic vasoconstrictor responses to ANG I but not to ANG II. Early onset treatment with high-dose ramipril increased aortic vasodilatory responses to acetylcholine and decreased vasoconstrictor responses to noradrenaline. Treatment of adult SHR for 16 weeks with high-dose ramipril (regression study) had similar effects on vascular function, but did not affect vascular hypertrophy (see above). Low-dose ramipril, although having no effect on blood pressure, significantly decreased the aortic vasoconstrictor responses to noradrenaline in both the prevention and the regression study. This regimen further increased the vasodilatory responses to acetycholine in the regression study and to a more limited extent in the prevention study. Low and high dose ACE inhibitor treatment resulted in a significant increase in aortic cyclic GMP by 98 and 160% respectively [63].

In a more recent study in stroke prone SHR by long term treatment with ramipril, an increased myocardial contractility and coronary flow, reduced release of lactate dehydrogenase and creatine kinase into the coronary effluent and increased myocardial tissue levels of glycogen as well as the energy rich phosphates ATP and creatine phosphate in isolated hearts of these animals were observed [49]. These changes in cardiodynamics and cardiac metabolism were observed even at the low dose of ramipril which did not affect blood pressure and LVH. The beneficial changes could be prevented by chronic kinin receptor blockade with icatibant (Fig. 2). Thus, the observed cardiac effects of the ACE inhibitor were independent of blood pressure reduction and due to its kinin potentiating action.

Chronic NO synthase inhibition in rats

Endothelium-derived NO is an important modulator of vascular tone [64], and inhibition of its generation may be achieved using arginine analogues such as N^G-nitro-L-arginine-methyl ester (L-NAME) [65]. In the rat, acute administration of L-NAME is associated with a dose-dependent increase in arterial pressure and total vascular resistance [66, 67]. Recently, it has been reported that long-term inhibition of NO synthase will produce a sustained hypertension in otherwise normotensive rats and dogs [68–71], thus providing a new experimental model of hypertension and hypertrophy.

To evaluate the cardiac effects of ramipril on L-NAME-induced hypertension in rats we focused our interest on myocardial hypertrophy, dynamics and metabolism.

Chronic treatment with L-NAME in a dose of 25 mg/kg per day over 6 weeks caused myocardial hypertrophy and a significant increase in systolic blood pressure as compared to controls. Animals receiving simultaneously L-NAME and ramipril were protected against blood pressure increase and partially against myocardial hypertrophy [72] (Fig. 3).

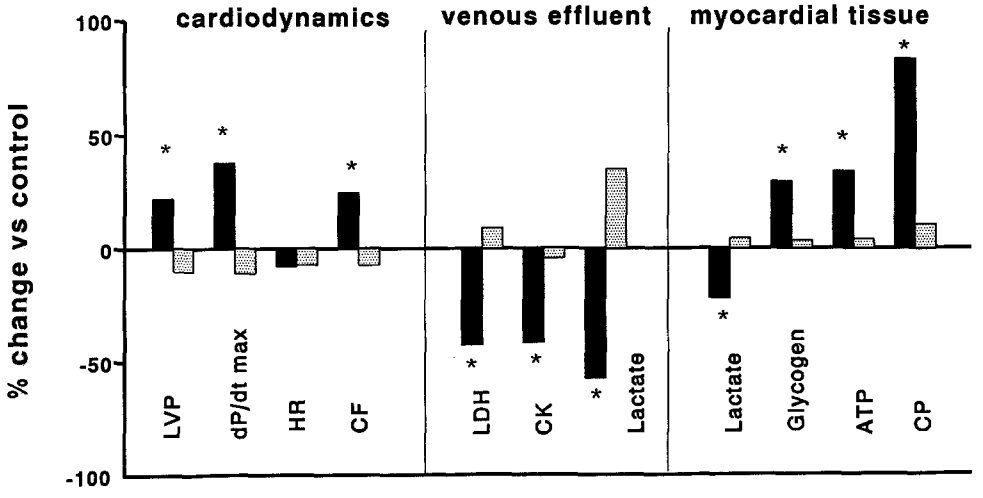

Fig. 2. Effect of chronic oral treatment, prenatally and subsequently up to the age of 20 weeks, with low dose ramipril (10 μg/kg/day) alone (black bars) and after cotreatment with the kinin receptor antagonist icatibant (500 μg/kg/day s.c.) (dotted bars) on myocardial function and metabolism in isolated perfused hearts from stroke prone spontaneously hypertensive rats (SHRSP). LVP indicates left ventricular pressure: dP/dt_{max}, differentiated left ventricular pressure; HR, heart rate; CF, coronary flow; LDH, lactate dehydrogenase; CK, creatine kinase; and CP, creatine phosphate. *$p < 0.05$ compared with vehicle control group.

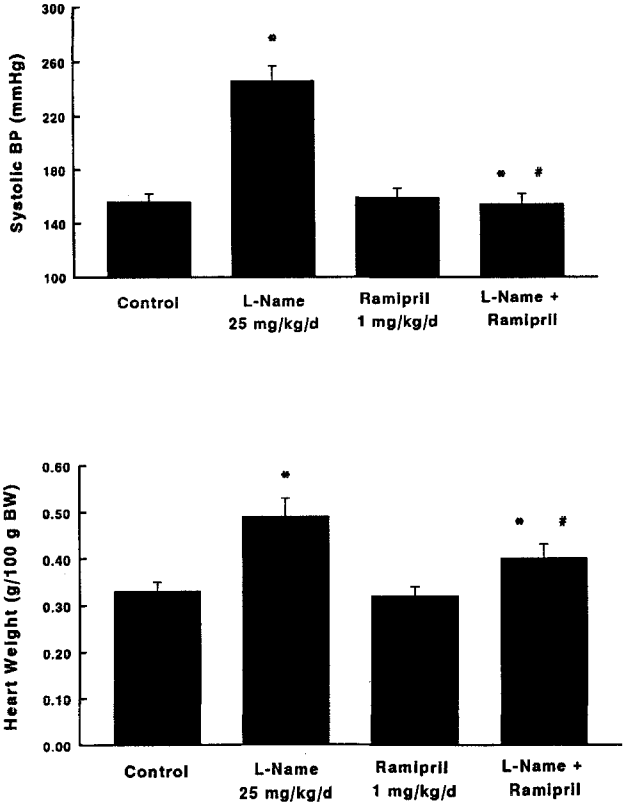

Fig. 3. Effect of oral L-NAME (25 mg/kg/day) and ramipril (1 mg/kg/day) treatment over 6 weeks as well as the combination of both on systolic blood pressure and heart weight in Wistar rats. *p < 0.05 vs. control, #p < 0.05 vs. L-NAME group.

Isolated hearts from these rats treated with L-NAME showed increased post-ischemic reperfusion injuries. Compared to controls duration and incidence of ventricular fibrillation was increased and coronary flow reduced. During ischemia the cytosolic enzymes lactate dehydrogenase and creatine kinase, as well as lactate in the venous effluent were increased. Myocardial tissue values of glycogen, ATP, and creatine phosphate were decreased, whereas lactate content was increased. Coadministration of ramipril reversed these effects.

Due to suppression of the modulating influence of NO by L-NAME, vasoconstrictor effects of ANG II may prevail. On the other hand, NO and PGI_2, when increased by inhibiting breakdown of BK and related kinins after ACE inhibition may contribute to the beneficial cardioprotective effects [73].

Conclusion

The cardiovascular actions of ACE inhibitors are not only mediated by reduction of ANG II but also by the inhibition of the degradation of endogenous BK and related kinins. This is evidenced by the comparable effects of ACE inhibitors and exogenously added BK in different physiological and pathophysiological situations and by the observation that the kinin receptor antagonist icatibant blocked the cardiovascular effects of ACE inhibitors as well as of BK in experimental models of LVH. The increase in local kinin concentrations by ACE inhibition exerts protective effects activating signal transduction pathways which generate second messengers such as cyclic GMP via an increase in NO or cyclic AMP via an increase in PGI_2 [73].

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