Chronic effects of early started angiotensin converting enzyme inhibition and angiotensin AT\textsubscript{1}-receptor subtype blockade in rats with myocardial infarction: role of bradykinin

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Abstract

Objective: The long-term effects and mechanisms of early started angiotensin converting enzyme (ACE) inhibition post myocardial infarction (MI) are not well understood. Chronic effects of early ACE inhibition on hemodynamics, left ventricular diastolic wall stress and remodeling were, therefore, compared to that of angiotensin AT\textsubscript{1}-receptor subtype blockade in rats with experimental myocardial infarction. The contribution of bradykinin potentiation to both ACE inhibitor and angiotensin AT\textsubscript{1}-receptor subtype blockade was assessed by cotreatment of rats with a bradykinin B2-receptor antagonist.

Methods: MI was produced by coronary artery ligation in adult male Wistar rats. The ACE inhibitor, quinapril (6 mg/kg per day), or the angiotensin AT\textsubscript{1}-receptor subtype blocker, losartan (10 mg/kg per day), administered by gavage, and the bradykinin B2-receptor antagonist, Hoe-140 (500 \textmu g/kg per day s.c.), administered either alone or in combination with quinapril or losartan, were started 30 min after MI and continued for eight weeks. Results: Quinapril and losartan reduced left ventricular end-diastolic pressure and global left ventricular diastolic wall stress only in rats with large MI. Pressure volume curves showed a rightward shift in proportion to MI size that was not prevented by quinapril or losartan treatment. Only the ACE inhibitor reduced left ventricular weight and this effect was prevented by cotreatment with Hoe-140, suggesting an angiotensin II blockade-independent, but bradykinin potentiation-dependent, mechanism.

Keywords: Myocardial infarction; Remodeling; ACE-inhibition; AT\textsubscript{1}-receptor; Bradykinin; Rats

1. Introduction

Angiotensin converting enzyme (ACE) inhibitors are beneficial in the prevention of left ventricular dilatation, heart failure and death post myocardial infarction [1–3]. Left ventricular dilatation appears to play a key role in the development of heart failure [1,2,4–6] and for prognosis [7] in patients after a large infarct. The potential for progressive ventricular dilatation exists from the time of coronary occlusion and infarction [4,5,8–13]. It might be important, therefore, to start ACE inhibitor therapy as soon as possible after myocardial infarction (MI) [1,14–16]. However, it could also block early compensatory mechanisms, including early compensatory left ventricular dilatation [5]. Treatment with captopril 2 h, two days or three weeks after acute MI has beneficial effects in the rat MI model [1,2,17]. In contrast, in the clinical CONSENSUS II
study [18], treatment with enalapril was started within 24 h of acute MI, but patients showed no improvement in survival over the 180 days after infarction. In contrast, the acute application of ACE inhibitors along with thrombolitic therapy showed some survival benefits as early as five–six weeks after the infarct [19,20]. Thus, the long-term effects of early started treatment with ACE inhibitors post infarct are not well understood.

In addition, it remains unclear so far whether or not the effect of ACE inhibitors is mediated by prevention of angiotensin II (AII) generation. All receptor-independent effects have also been suggested [21–23]. Specific AII receptor antagonists have only recently become available [24]. Raya et al. [24] reported that treatment for two weeks with captopril or the AII receptor antagonist losartan, initiated three weeks after large infarction in rats, decreased left ventricular end-diastolic pressure and left ventricular end-diastolic volume index and increased venous compliance. These data suggested that specific blockade of AII was sufficient to explain the benefits of ACE inhibitors. Smits et al. [25], who started treatment during (1–21 days) and after (21–35 days) completion of the repair phase of MI, suggested that the effects of captopril in rats after MI were not dependent on AII. Most recently, Schieffer et al. [26] suggested similar effects of ACE inhibition and angiotensin AT₁-receptor subtype blockade in preventing important features of ventricular remodeling after MI. Moreover, it is suggested that multiple actions relevant to cardiovascular control of ACE inhibitors were related in part to bradykinin potentiation, and cotreatment with a bradykinin receptor antagonist abolished all ACE inhibitor-induced effects on cardiac function in stroke-prone spontaneously hypertensive rats [27]. Finally, the important role of myocardial infarct size has not been analyzed for the effect of early treatment with ACE inhibitors or AII receptor antagonists. It remains unclear so far why ACE inhibitors reduced left ventricular volume only in animals with large infarcts [1]. Therefore, we studied the chronic effects on hemodynamics, left ventricular volume and wall stress of ACE inhibition by quinapril2.3. Losartan only in animals with large infarcts [1]. Therefore, we either drug was equipotent (Fig. 1).

In pilot experiments, the pressor response to angiotensin I (AI) of the applied quinapril and losartan dosage was tested. Rats were pretreated with quinapril (6 mg/kg/day), a group treated with losartan (10 mg/kg), a group treated with Hoe-140 (500 μg/kg/day), a group treated with quinapril plus Hoe-140, and a group treated with losartan and Hoe-140. According to the extent of the histologic infarct size, an additional four subgroups were established in each treatment group. These included rats in which failure of ligation of the coronary artery occurred (sham), in which infarcts were less than 30% (small), ranged from 30 to <45% (moderate) or were 45% and larger (large). Treatments were started by gavage 30 min after coronary artery ligation or sham operation and were repeated daily for eight weeks. Animals were housed in polyethylene cages in climatized rooms with a 12-h light–dark cycle and fed with standard laboratory food and tap water.

2.2. Angiotensin I dose–response curves

In pilot experiments, the pressor response to angiotensin I (AI) of the applied quinapril and losartan dosage was tested. Rats were pretreated with quinapril (6 mg/kg body weight, n=5), losartan (10 mg/kg body weight, n=5) or water (n=5) and AI (1–25 μg/kg/min) was infused 6 h after the respective treatment. The dose–response curves demonstrated that the inhibition of AI pressor response by either drug was equipotent (Fig. 1).

2.3. Hemodynamic measurements and left ventricular volume

Eight weeks after coronary artery ligation, rats were reanesthetized with ether. Polyethylene cannulas were inserted into the trachea for artificial ventilation, into the right carotid artery and jugular vein, and into a femoral vein. Pressures were measured through a short segment of fluid-filled PE 50 tubing, connected to a microtip manometer (Millar®) via a three-way stopcock, with zero adjusted to mid-chest level. The carotid cannula was briefly advanced into the left ventricle, then withdrawn to the aortic arch while pressures were recorded. The jugular vein cannula was advanced to the right atrium. Left ventricular systolic pressure (LVSP) and end-diastolic pressure (LVEDP), the maximum rate of rise of left ventricular systolic pressure, dP/dt_{max}, the mean arterial pressure (MAP), heart rate (HR) and the mean right atrial pressure

2. Methods

2.1. Animals, experimental myocardial infarction and pharmacologic interventions

Adult male Wistar rats, weighing 280–300 g when the study was started, were used and coronary artery ligation was performed as described previously by Pfeffer et al. [1]. In brief, rats were anesthetized by ether, intubated and ventilated by a volume-constant rodent ventilator (UB 7025 rodent ventilator, Hugo Sachs Elektronik, March, Germany), and a left thoracotomy was performed. The heart was exteriorized from the thorax, and the left coronary artery was ligated using a 5.0 suture between the pulmonary artery outflow tract and the left atrium. The heart was then returned to its normal position and the thorax was closed. All procedures conformed to the “Position of the American Association on Research Animal Use” and were approved by the institutional animal research committee.

Twenty-four groups of rats were studied: The six treatment groups included untreated control rats, a group treated with quinapril (6 mg/kg/day), a group treated with losartan (10 mg/kg), a group treated with Hoe-140 (500 μg/kg/day), a group treated with quinapril plus Hoe-140, and a group treated with losartan and Hoe-140. According to the extent of the histologic infarct size, an additional four subgroups were established in each treatment group. These included rats in which failure of ligation of the coronary artery occurred (sham), in which infarcts were less than 30% (small), ranged from 30 to <45% (moderate) or were 45% and larger (large). Treatments were started by gavage 30 min after coronary artery ligation or sham operation and were repeated daily for eight weeks. Animals were housed in polyethylene cages in climatized rooms with a 12-h light–dark cycle and fed with standard laboratory food and tap water.
(RAP) were measured under light ether anesthesia and spontaneous respiration.

During positive pressure ventilation, and after midsternal thoracotomy, a calibrated flowmeter (2.5 mm; Statham) was placed around the ascending aorta for continuous measurement of aortic blood flow. Mean aortic blood flow was obtained electronically and taken as the cardiac index (CI), as described by Pfeffer et al. [1]. The systemic vascular resistance index (SVRI) was calculated as (MAP−RAP)/CI and was expressed as mmHg/ml/min/kg body weight.

After baseline measurements, warmed (39–40°C) Tyrode’s solution was infused into a femoral vein at a rate of 40 ml/kg/min for 45 s or until maximal flow was achieved [1]. This infusion produced a rise in cardiac output to peak values, followed by a plateau, despite further elevation of right atrial pressure. Maximum cardiac performance was defined as peak values of cardiac output (CI\textsubscript{max}) and stroke volume (SVI\textsubscript{max}) during this infusion of Tyrode’s solution.

Ten to 15 min after the volume load, when all hemodynamic variables had returned to baseline levels, the flowmeter was removed and the arterial catheter was advanced into the left ventricle. The ascending aorta was briefly occluded around the catheter by a suture, to produce contractions that were isovolumic except for coronary flow. Measurements were made of left ventricular peak systolic and end-diastolic pressure. Maximal left ventricular developed pressure was calculated as the peak systolic minus end-diastolic pressure during aortic occlusion. These measurements defined the maximal pressure-generating ability of the left ventricle, as previously described [28]. Then, a second volume loading was applied to determine the peak left ventricular end-diastolic pressures.

The passive pressure–volume curves of the left ventricle were obtained as previously described [6]. The heart was arrested using potassium chloride and a double-lumen catheter (PE 50 inside PE 200) was inserted into the left ventricle via the ascending aorta. The right ventricular free wall was incised to avoid fluid accumulation. The atrioventricular groove was ligated and isotonic saline was infused at a rate of 0.76 ml/min via one lumen, while intraventricular pressure was continuously recorded through the other lumen, from negative pressure to 30 mmHg. Three reproducible pressure–volume curves were obtained within 10 min of cardiac arrest, well before the onset of rigor mortis. The operating left ventricular end-diastolic volume was derived from the left ventricular pressure–volume curve [1,15]. It was defined as the volume on the pressure–volume curve corresponding to a filling pressure equal to in vivo end-diastolic pressure. Analysis of global ventricular wall stress was performed using volume measurements from the pressure–volume relationship and a spherical model for ventricular geometry, as described by Teerlink et al. [29]. Diastolic wall stress (\(\sigma_d\)) = \(P(\alpha^2/\beta^2-a^2)\), where \(P=\text{LVEDP (mmHg)}\), \(a\) is the internal radius, measured as \((3/4\times\text{ventricular volume})^{1/3}\), and \(b\) is the outer radius, measured as \((3/4[\text{ventricular volume}+(1.05 \text{ ml/g}\times\text{ventricular mass})])^{1/3}\).

### 2.4 Infarct size

The method used to process the heart for the measurement of infarct size was similar to that previously described [1,30]. After the pressure–volume data had been recorded, the hearts were fixed in distended form in 10% buffered formalin for 24 h, then dissected into left ventricle plus interventricular septum and right ventricular free wall, which were weighed separately. The whole left ventricle was dehydrated in alcohol, cleared in xylene, and embedded in paraffin. Transverse serial sections of 20 μm thickness were obtained in 1 mm intervals from apex to base, mounted and stained with phosphotungstic acid–hematoxylin so that necrotic infarct tissue stained red and non-infarcted myocardium blue. The slices were projected and the lengths of infarct and total left ventricle on both epicardial and endocardial surfaces of each section were measured using a calibrated digitizer (Numonics Digitizer 2200®). Infarct size was calculated by dividing the sum of the planimetered endocardial and epicardial circumference occupied by the infarct by the sum of the total epicardial and endocardial circumferences of the left ventricle.

### 3. Data analysis

Results are expressed as mean:±SEM. Statistical comparisons among infarct and treatment groups were evaluated by ANOVA and significant difference was determined by the Bonferroni test. \(P<0.05\) was considered to indicate statistical significance. For the difference in mortality, Kaplan–Meier–Survival analysis was performed and dif-
ferences between the groups were tested for significance by the log-rank statistic using the Cox–Mantel test.

4. Results

A total of 723 rats underwent coronary artery ligation or sham operation, 114 rats in the control group, 150 rats in the quinapril treatment group, 119 rats in the losartan treatment group, 117 rats in the Hoe-140 treatment group, 99 rats in the quinapril plus Hoe-140 treatment group and 124 rats in the losartan plus Hoe-140 treatment group. No differences in mortality during the eight weeks were found among control, quinapril- or losartan-treated rats (48% in control, 53% in quinapril treated, 50% in losartan treated group, 48% in Hoe-140 treated group, 43% in quinapril plus Hoe-140 treated group and 46% in losartan plus Hoe-140 treated group). Infarct sizes were similar among the various treatment groups (Table 1).

4.1. Body weights and ventricular weights

Body weights and ventricular weights are shown in Table 2. Quinapril reduced left ventricular weight, and left ventricular weight to body weight ratio, significantly in sham rats and rats with small MI and these effects were abolished by cotreatment with Hoe-140. Right ventricular weight to body weight ratio was increased in untreated rats with large MI. Hoe-140 increased right ventricular weight, and quinapril reduced it, in rats cotreated with Hoe-140.

4.2. Hemodynamic measurements prior to thoracotomy

As shown in Table 3, LVSP tended to be lower in rats with moderate and large MI sizes compared to the respective sham rats, and to be decreased by quinapril and losartan, respectively. These changes were not affected by cotreatment with Hoe-140. MAP showed similar changes after quinapril and losartan. dP/dt max was lower in rats with large MI in the untreated group, but was preserved to some extent in quinapril- and losartan-treated animals; cotreatment with Hoe-140 abolished these effects. LVEDP was increased in untreated rats with large MI. Both quinapril and losartan significantly decreased LVEDP versus untreated rats with large MI, again, these effects were abolished by cotreatment with Hoe-140. Hoe-140 alone increased LVEDP. RAP was increased by large MI, reduced by quinapril and losartan, and not affected by Hoe-140. Heart rate was similar in all groups of rats studied (not shown).

4.3. Hemodynamic measurements at baseline

As shown in Table 4, MAP was somewhat lower after thoracotomy than before it (Table 3). Infarction reduced
the CI and SVI in proportion to infarct size. Quinapril prevented this reduction of CI and SVI post-infarction, while losartan did not. The total peripheral resistance index (TPRI) was increased in untreated rats with moderate and large MI, and both quinapril and losartan significantly reduced TPRI, however, the effect was more pronounced after quinapril and consistent throughout all groups with infarction. After cotreatment with Hoe-140, the effect of quinapril on CI was abolished but the effect of quinapril on TPRI was not affected.

4.4. Peak cardiac performance

Peak CI and SVI (Table 5) were reduced in untreated rats in proportion to infarct size. These parameters were not affected by losartan, however, quinapril prevented this reduction of CI and SVI. Peak LVEDP during volume loading was increased by large MI in untreated rats. Both quinapril and losartan tended to prevent the increase in peak LVEDP by large MI. Peak developed pressure was decreased in proportion to infarct size in untreated rats.
Quinapril or losartan treatment reduced peak developed pressure in sham rats and in rats with small MI, but not in rats with moderate or large MI. The ratio of peak developed left ventricular pressure to left ventricular weight also decreased in untreated rats with moderate and large MI. The reduction of developed pressure by quinapril and losartan in sham-operated animals disappeared after correction for left ventricular weight. The effects on peak CI after quinapril, and decreased peak LVEDP by quinapril and losartan, in rats with large MI were abolished after cotreatment with Hoe-140.

4.5. Left ventricular volume

Pressure volume curves showed a rightward shift in proportion to MI size in untreated rats, which was not affected by quinapril or losartan treatment or by cotreatment with Hoe-140 (not shown). Operating left ventricular volume and its ratio to left ventricular weight are shown in Fig. 2A–B. Volume was significantly increased in untreated rats with moderate or large MI, significantly reduced by quinapril and tended to be reduced by losartan treatment in rats with large infarction. These effects were partially abolished after cotreatment with Hoe-140 in the quinapril group and were completely abolished in the losartan group.

4.6. Left ventricular diastolic wall stress

Diastolic wall stress (Fig. 3) significantly increased only in animals with large infarcts and, in these animals, only quinapril and losartan significantly reduced wall stress. Quinapril reduced diastolic wall stress to about 30% in animals with large infarcts, despite treatment with Hoe-140.
5. Discussion

The study failed to show a prevention of structural dilatation of the left ventricle when therapy with an ACE inhibitor or AII receptor antagonist was started 30 min after coronary occlusion. The study is limited to permanent coronary occlusion and may not apply to the clinical situation when reperfusion may be achieved. Neither quinapril nor losartan had an effect on infarct size or mortality, as tested for the total groups. The study answers in part the question of why ACE inhibitors prevent left ventricular dilatation only in certain subgroups of individuals with myocardial infarction. Pfeffer et al. [1] reported a reduction in left ventricular operating volume only in rats with large infarcts. In the present study, both the ACE inhibitor and the AII receptor antagonist reduced diastolic wall stress only in animals with large infarcts. In addition, the study shows basic differences between the

Table 5
Peak cardiac performance

<table>
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<th>Sham</th>
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<td></td>
<td>Small (&lt;30%)</td>
<td>Moderate (≥30%&lt;45%)</td>
<td>Large (≥45%)</td>
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<td>CI&lt;sub&gt;max&lt;/sub&gt; (ml/min/kg)</td>
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<td>Untreated</td>
<td>433 ± 14</td>
<td>366 ± 23&lt;sup&gt;a&lt;/sup&gt;</td>
<td>296 ± 23&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Quinapril</td>
<td>395 ± 21</td>
<td>371 ± 17</td>
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<td>HOE-140</td>
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<td>416 ± 15</td>
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<td>0.76 ± 0.06&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>214 ± 6</td>
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CI<sub>max</sub>, peak cardiac index attained during volume loading.

SVI<sub>max</sub>, peak stroke volume index attained during volume loading.

DEVP<sub>max</sub>, peak developed pressure attained during aortic occlusion.

DEVP<sub>max</sub>/LV peak developed pressure attained during aortic occlusion-to-left ventricular weight ratio.

LVEDP<sub>max</sub>, peak left ventricular end-diastolic pressure corresponding to the peak stroke volume index attained during volume loading.

<sup>a</sup> p<0.05 vs. sham in the same treatment group.

<sup>b</sup> p<0.05 vs. untreated rats with comparable infarct size.

Numbers are expressed as the mean±SEM.
Fig. 2. Operating left ventricular volume (A) and operating left ventricular volume-to-left ventricular weight ratio (B) in placebo-treated rats (open bars), quinapril-treated rats (hatched, rising right), losartan-treated rats (hatched, rising left), Hoe-140-treated rats (crosshatched), quinapril plus Hoe-140-treated rats (Q+Hoe-140, horizontally hatched) and losartan plus Hoe-140-treated rats (L+Hoe-140, vertically hatched). Data are shown as mean±SEM.

* p<0.05 vs. sham rats in the same treatment group; † p<0.05 vs. untreated rats with comparable infarct size; ‡ p<0.05 vs. quinapril-treated rats with comparable infarct size; ‖ p<0.05 vs. Hoe-140-treated rats with comparable infarct (MI) size.
ACE inhibitor and the angiotensin AT_1-receptor subtype antagonist. First, the ACE inhibitor reduced systemic vascular resistance independently of infarct size, while the angiotensin AT_1-receptor subtype blocker reduced resistance only in animals with moderate or large infarcts. Second, only the ACE inhibitor significantly reduced left ventricular weight. Third, only the ACE inhibitor increased the cardiac index in rats with large infarcts. A striking effect of the bradykinin antagonist Hoe-140 was that it increased LVEDP in all animal groups, including sham-operated animals. Perhaps as a consequence of an increased right ventricular afterload, Hoe-140 substantially increased right ventricular weight. In contrast, Hoe-140 did not change systemic vascular resistance or right atrial pressure and did not prevent the vasodilator effects of quinapril or losartan. Left ventricular weight reduction and an increase in the cardiac index by the ACE inhibitor was abolished by the bradykinin antagonist.

5.1. Weights, volume and wall stress

Myocardial infarction induced hypertrophy of surviving myocardium, as suggested by unchanged left ventricular weight in the presence of reduced free wall (scar) thickness and increased septal thickness [31]. One limitation of this and other studies is that we used weight to estimate "hypertrophy" [1,17,24-26]. As shown previously, structural left ventricular dilatation occurred in proportion to infarct size [1,6,31,32].

Our data, together with those in the literature, suggest that ACE inhibitors, in a manner that is independent of the specific type of drug and the timing of treatment, prevent hypertrophy of surviving myocardium or produce some type of "atrophy" in sham-operated animals [1,17,26]. The pathophysiologic consequence of the latter remains dubious. In contrast, the angiotensin AT_1-receptor subtype blocker, losartan, had no effect on left ventricular weight. The conflicting reports on the effect of ACE inhibitors and angiotensin AT_1-receptor subtype blockers on heart weight post MI may be due to various doses and timings of treatments or the effects of ACE inhibitors that are independent of AII [24-26,33-35]. Our data suggest that, in this model, in contrast to the situation in the spontaneously hypertensive rat (SHR) [36] or due to volume overload induced by aortocaval shunt [37], AII does not act as a growth promoting factor [38] by stimulation of the AT_1 receptor blocked by losartan. Systolic load (LVSP, MAP, TPRI) was somewhat lower with quinapril than with
losartan only in animals with MI, and diastolic wall stress was identical (see below). Thus, differences in mechanical factors may not conclusively explain differences between the drug effects on LV weight. The ACE inhibitor may interfere with hypertrophy [1,15,16,39,40] by bradykinin potentiation [21–23], prostaglandins and EDRF (NO) release [41,42]. In fact, decreased LV-to-body weight ratios, elicited by quinapril in sham rats and rats with small MI, were restored after cotreatment with Hoe-140, supporting a role of bradykinin potentiation by the ACE inhibitor for prevention of hypertrophy in this model. McDonald et al. also showed that the antigrowth effect of the ACE inhibitor ramipril was prevented in the direct current shock model in dog by cotreatment with Hoe-140 [43]. The striking gain of right ventricular weight caused by Hoe-140 may also reflect, in part, prevention of the “antitrophic” effects of bradykinin.

Neither quinapril nor losartan treatment showed a significant effect on the rightward shift of the in situ obtained pressure volume curve of arrested left ventricles or of ventricular diameters determined in vitro. End-diastolic volume at in vivo left ventricular end-diastolic pressure (“operating volume”) was, however, reduced by quinapril and tended to be lowered by losartan in rats with large myocardial infarcts (Fig. 2A). This effect was primarily the result of a decrease in left ventricular end-diastolic pressure. Previous studies using ACE inhibitors in different protocols post myocardial infarction have also reported major effects on the operating left ventricular volume rather than on the pressure–volume curve [1,24]. Importantly, however, the operating left ventricular volume-to-weight ratio (Fig. 2B) was also decreased in rats with large MI by quinapril and, again, tended to be lowered by losartan, suggesting decreased wall stress. Chronic bradykinin B2 receptor blockade with Hoe-140, as mentioned above, substantially increased LVEDP and resulted in higher LVEDP also in animals treated with quinapril and losartan. However, both quinapril and losartan tended to reduce LVEDP even in animals treated with Hoe-140, suggesting that this effect was not exclusively mediated by bradykinin.

An estimate of global diastolic wall stress, as previously described by Teerlink et al. [29], increased 30-fold in animals with large infarcts vs. sham-operated animals, and was reduced to one fourth by quinapril and, again, tended to be lowered by losartan, suggesting decreased wall stress. Chronic bradykinin B2 receptor blockade with Hoe-140, as mentioned above, substantially increased LVEDP and resulted in higher LVEDP also in animals treated with quinapril and losartan. However, both quinapril and losartan tended to reduce LVEDP even in animals treated with Hoe-140, suggesting that this effect was not exclusively mediated by bradykinin.

6. Quinapril versus losartan

6.1. Similarities

Both losartan and quinapril had vasodilator properties...
that were pronounced or only occurred in animals with large infarcts. Since these effects were not affected by a bradykinin antagonist, they depended, at least in part, on a similar antagonism of both drugs to the renin–angiotensin system. Both drugs also reduced the left ventricular operating volume in animals with large infarcts, in which quinapril had more consistent effects, suggesting an interdependence between their systemic hemodynamic and volume effects. Most importantly, both drugs reduced diastolic wall stress only in animals with large infarcts.

6.2. Dissimilarities

One major difference between the drugs was that only quinapril reduced left ventricular weight and prevented hypertrophy. This appeared to be independent of infarction and of activation of the renin–angiotensin system and could be attributed to a bradykinin-potentiating action of ACE inhibitor, since it was prevented by cotreatment with Hoe-140. The other major difference was that only quinapril restored cardiac index in rats with large infarction. The reason for this difference could not be clarified by this study and could only be addressed by dose–response curves for both drugs. The fact that restoration of cardiac performance by quinapril could be partially abolished by cotreatment with Hoe-140 may support a role of bradykinin in this respect. Prevention of sodium and water retention may also be involved in changing the loading conditions of the heart. One possible explanation for a discrepancy between the effects of quinapril and losartan might therefore be that they are indeed not related to All antagonism.

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