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Cardioprotective effects of quinapril after myocardial infarction in hypertensive rats

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Abstract

Although angiotensin-converting enzyme inhibitors are beneficial for patients with congestive heart failure, the appropriate timing and dosage in acute myocardial infarction are still controversial. We examined the hemodynamic effects of quinapril administered before acute myocardial infarction in spontaneously hypertensive rats (SHR). Quinapril (10 mg/kg per day in drinking water) was started 1 week before infarction and continued for 4 weeks after infarction (total duration 5 weeks). The hemodynamic parameters were evaluated by cardiac catheterization 4 weeks after coronary ligation. Sham-operated SHR served as controls. After infarction, left ventricular end-diastolic and right atrial pressures were increased ($P < 0.01$) and blood pressure and cardiac index were decreased ($P < 0.01$); the magnitude of blood pressure reduction was similar in the treated and untreated rats with infarction. Quinapril improved these hemodynamic parameters significantly and decreased left and right ventricular weight. These results suggest that a prior treatment with quinapril in SHR with acute myocardial infarction is hemodynamically beneficial.

Keywords: Cardiac hypertrophy; Heart failure; Hypertension; Renin–angiotensin system

1. Introduction

Although angiotensin-converting enzyme inhibitors are now accepted as the drug of choice in the treatment of congestive heart failure, their efficacy after acute myocardial infarction is less equivocal. Angiotensin-converting enzyme inhibition was beneficial in patients with myocardial infarction when the treatment was started several days after the episode (Cleland et al., 1997; SAVE Investigators, 1992). Some studies, however, showed deleterious effects of angiotensin-converting enzyme inhibitors if initiated immediately after infarction both in humans (Swedberg et al., 1992) and rats (Schoemaker et al., 1991). These results raise concern that angiotensin-converting enzyme inhibitors may induce unfavorable hypotension and disturb the initial healing processes or cardiac remodeling, resulting in deteriorated cardiac function and no improvement in mortality. Thus, the appropriate timing and dosage of angiotensin-converting enzyme inhibitors after myocardial infarction are still controversial.

Hypertension is one of the risk factors for coronary artery disease. Patients with hypertension often develop left ventricular hypertrophy. The hemodynamic deterioration after acute myocardial infarction appears to be more marked in the hypertrophied heart than in the normal heart (Fletcher et al., 1982; Nishikimi et al., 1995). Angiotensin-converting enzyme inhibitors are commonly used in the treatment of hypertension, particularly when left ventricular hypertrophy is present, and some of the patients with angiotensin-converting enzyme inhibitor treatment may develop acute myocardial infarction. However, there are few reports on the effect of angiotensin-converting enzyme inhibitors administered before myocardial infarction in the hypertrophied heart.

Objective of this study was to determine whether a pretreatment with a depressor dosage of quinapril in spontaneously hypertensive rats (SHR) had beneficial effects on cardiac function after acute myocardial infarction induced by coronary artery ligation. Quinapril was started 1 week before infarction and continued for 4 weeks thereafter. Hemodynamic study under anesthesia revealed that quinapril improved cardiac performance without any adverse effects.

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2. Materials and methods

2.1. Animal preparation

Male SHR/Izm were obtained from the Disease Model Cooperative Research Association (Kyoto, Japan) at 12 weeks of age. They were kept at a controlled room temperature under 12:12 h light/dark cycle and fed standard rat chow. Since 16 weeks of age, systolic blood pressure in conscious rats was measured every week by the tail-cuff method (UR-1000, Ueda, Tokyo, Japan), as described before (Nishimura et al., 1992). At 19 weeks of age, rats were randomly assigned to the treated and untreated groups. After 1-week treatment with quinapril, these 2 groups were subdivided into the sham operation and myocardial infarction groups. Treatment was continued for another 4 weeks after myocardial infarction. All protocols were approved by the Ethical Committee of the Osaka Medical College.

2.2. Drug administration

Quinapril was freshly dissolved in drinking water and administered to rats at 10 mg/kg per day. Body weight and water intake were measured weekly to allow adjustment of the drug concentration. Untreated animals received tap water alone. This dose of quinapril significantly decreased blood pressure in SHR (Albaladejo et al., 1994). We used quinapril because it has a strong affinity for cardiac renin–angiotensin system (Kinoshita et al., 1993; Nakajima et al., 1992).

2.3. Myocardial infarction

At 20 weeks of age, after 1-week treatment, myocardial infarction was produced by a method previously described (Nishikimi et al., 1995; Stauss et al., 1994) and modified in our laboratory. In brief, under pentobarbital anesthesia (30 mg/kg i.p.), rats were intubated and connected to a volume regulated ventilator (Model 683, Harvard Apparatus, USA). A left thoracotomy was done in the fourth intercostal space and the left coronary artery 2–3 mm from its origin was ligated using 5-0 prolene suture. The heart was restored to the normal position and the chest was closed. To reduce deaths due to lethal arrhythmias, we pretreated rats with xylocaine (1–2 mg/kg i.p.) before coronary ligation and observed the electrocardiogram throughout the procedure. When ventricular tachycardia or ventricular fibrillation developed, we injected additional xylocaine or tapped the chest gently as soon as possible. A sham-operated group underwent the same surgical procedure except for coronary ligation.

2.4. Hemodynamics

At 24 weeks of age, cardiac catheterization was performed under pentobarbital anesthesia (50 mg/kg i.p.) as described elsewhere (Nishimura et al., 1992). A 2F catheter-tip micromanometer (Model PR-249, Millar Instruments, Houston, TX, USA) was introduced via the right carotid artery into the ascending aorta and left ventricular cavity to measure aortic and left ventricular systolic and diastolic pressures, dp/dt and heart rate. These parameters were recorded at a paper speed of 100 mm/s on a multi-channel recorder (Rectigraph-8K, San-Ei Instruments, Tokyo, Japan). Left ventricular end-diastolic pressure was displayed at a high sensitivity on an additional channel. A venous catheter (PE 50, Clay-Adams, New York, USA) connected to a micromanometer (model PR-249, Millar Instruments) was inserted through the right jugular vein into the right atrium to measure right atrial pressure. Cardiac output was obtained by the thermodilution method (Nishimura et al., 1992) using a computer (Cardiotherm 500, Columbus Instruments, Columbus, OH, USA). Cardiac index and total peripheral resistance index were calculated as follows:

Cardiac index = cardiac output/body weight.

Total peripheral resistance index

= mean aortic pressure/cardiac output/body weight.

Renal surface blood flow was obtained by laser-Doppler flowmetry using a probe (ALF 2100, Advance, Tokyo, Japan) placed on the surface of the left kidney (Nishimura et al., 1992).

2.5. Heart and kidney weight

Cardiac arrest was induced by 2% procaine (2 ml i.v.). The heart was rinsed with saline solution and blotted dry. After careful removal of the atria and great vessels, right and left ventricular weight was measured. Both kidneys were removed and the mean weight was determined. Relative values (organ weight/body weight) were used in the evaluation.

2.6. Surface area of the left ventricle and size of infarction

Infarct size was determined by a simple and reliable method (Nishikimi et al., 1995). In brief, incisions were made in the left ventricle so that the left ventricular tissue was pressed flat. The circumferences of the entire left ventricle and the region of infarction (scar portion) were outlined on a clear transparent plastic board for both the endocardial and epicardial surfaces. Both areas were measured by a computer. Infarct size was expressed as percentage of the scar portion to the entire left ventricular surface area. We evaluated a moderate size of infarction as described by Pfeffer et al. (1985): infarct sizes of less than 20% and over 40% were excluded from the study.

2.7. Statistics

All values are expressed as the means ± S.E.M. Data were first compared by analysis of variance. When signifi-

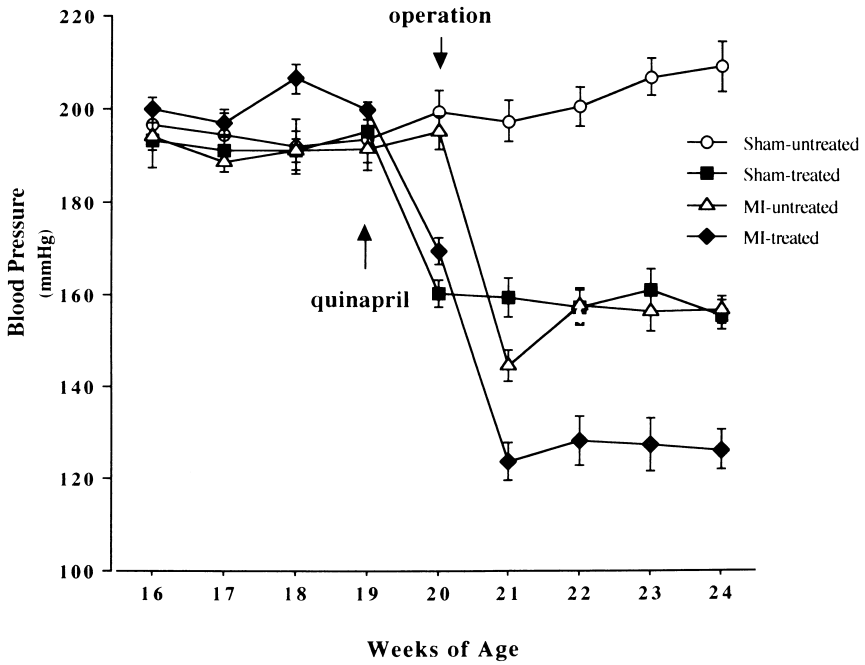

Fig. 1. Time course of blood pressure measurement in conscious rats. Quinapril decreased blood pressure in 19-week-old SHR by about 30 mmHg in 1 week. After myocardial infarction, blood pressure in the untreated and treated rats was similarly decreased by about 40 mmHg. MI, myocardial infarction.

cant differences were identified, the Scheffé's multiple range test was applied to determine the level of significance. P values < 0.05 were considered to be significant.

3. Results

3.1. Mortality and exclusions

The mortality in all rats including all sizes of myocardial infarction in the untreated and treated groups was 42 and 38%, respectively. There was no significant difference in the mortality. A total of 102 rats were initially used in this study, 56 of which were excluded due to death or small or large infarct sizes. Thus, a total of 46 rats were used for data analysis as being a moderate size of myocardial infarction. None of the sham-operated rats died.

3.2. Infarct size and left ventricular surface area

There was no significant difference in the infarct size in the untreated and treated groups (30.2 and 29.9%, respectively). Absolute infarct size was also not statistically different in the 2 groups (1.49 ± 0.05 vs. 1.22 ± 0.05

Table 1
Hemodynamic data obtained during cardiac catherization under pentobarbital anesthesia

	Sham	Sham	Infarction	Infarction
	Untreated ($n = 12$)	Treated ($n = 8$)	Untreated ($n = 15$)	Treated ($n = 11$)
Heart rate (beats/min)	363 ± 5	365 ± 6	337 ± 7	370 ± 10^{c}
Mean aortic pressure (mmHg)	179 ± 7	143 ± 7^{b}	135 ± 4^{b}	126 ± 6^{b}
LV systolic pressure (mmHg)	215 ± 9	171 ± 9^{b}	159 ± 5^{b}	150 ± 7^{b}
LV end-diastolic pressure (mmHg)	5.9 ± 0.4	4.3 ± 0.8^{d}	26.3 ± 1.8^{b}	9.7 ± 2.0^{d}
Right atrial pressure (mmHg)	2.4 ± 0.4	1.9 ± 0.2^{d}	7.0 ± 1.0^{b}	2.5 ± 0.3^{d}
Peak positive dp/dt (mmHg/s)	10075 ± 400	9013 ± 869^{d}	6353 ± 206^{b}	7782 ± 441^{b}
Peak negative dp/dt (mmHg/s)	9500 ± 399	9750 ± 372^{d}	4053 ± 172^{b}	$5618 \pm 383^{b,c}$
Cardiac index (ml/kg/min)	274 ± 14	294 ± 15^{d}	193 ± 10^{b}	297 ± 21^{d}
TPRI (mmHg min/ml per kg)	4.8 ± 0.3	3.5 ± 0.3^{c}	5.1 ± 0.3	$3.3 \pm 0.3^{b,d}$
Renal surface blood flow (ml/kg per min)	100 ± 4	94 ± 15	79 ± 7	105 ± 6

Data are expressed as means $\pm$ S.E.M. LV, left ventricular; RV, right ventricular; TPRI, total peripheral resistance index.
[a] $P < 0.05$ vs. untreated rats with sham operation.
[b] $P < 0.01$ vs. untreated rats with sham operation.
[c] $P < 0.05$ vs. untreated rats with infarction.
[d] $P < 0.01$ vs. untreated rats with infarction.

Table 2
Body, heart and kidney weight at 24 weeks of age

	Sham	Sham	Infarction	Infarction
	Untreated ($n = 12$)	Treated ($n = 8$)	Untreated ($n = 15$)	Treated ($n = 11$)
Body wt. (g)	375 ± 10	376 ± 8	379 ± 8	369 ± 11
Heart wt./body wt. (mg/g)	3.65 ± 0.07	$3.27 \pm 0.10^{a,d}$	4.17 ± 0.09^{b}	3.43 ± 0.06^{d}
LV wt./body wt. (mg/g)	3.09 ± 0.06	$2.62 \pm 0.08^{b,c}$	2.96 ± 0.09	$2.55 \pm 0.05^{b,d}$
RV wt./body wt. (mg/g)	0.56 ± 0.03	0.64 ± 0.04^{d}	1.21 ± 0.06^{b}	$0.87 \pm 0.05^{b,d}$
Kidney wt./body wt. (mg/g)	4.06 ± 0.04	4.16 ± 0.05	4.05 ± 0.07	4.00 ± 0.06

Data are expressed as means ± S.E.M. wt., weight; LV, left ventricular; RV, right ventricular.
[a] $P < 0.05$ vs. untreated rats with sham operation.
[b] $P < 0.01$ vs. untreated rats with sham operation.
[c] $P < 0.05$ vs. untreated rats with infarction.
[d] $P < 0.01$ vs. untreated rats with infarction.

cm^2). After infarction, left ventricular surface area was significantly increased (from 4.05 ± 0.16 to 4.93 ± 0.08 cm^2, $P < 0.01$), suggesting left ventricular dilatation. Quinapril normalized left ventricular surface area (4.19 ± 0.14 cm^2).

3.3. Hemodynamic data

Fig. 1 shows the time course of systolic blood pressure in conscious rats. Blood pressure of 19-week-old SHR before treatment was similar in each group. After 1-week treatment, quinapril decreased blood pressure significantly by about 30 mmHg. Compared with the sham-operated rats, blood pressure was significantly decreased in rats with infarction. Quinapril decreased blood pressure in these rats to the normotensive level. However, the magnitude of blood pressure reduction was similar in the treated and untreated rats after infarction (about 40 mmHg).

Table 1 summarizes the hemodynamic data obtained under pentobarbital anesthesia at 24 weeks of age. Heart rate tended to be lower in the untreated rats with infarction, which was normalized with quinapril. Quinapril in the sham-operated rats reduced aortic mean pressure and left ventricular systolic pressure but did not affect the other parameters. The untreated, infarcted rats had higher left ventricular end-diastolic pressure and right atrial pressure, and lower mean aortic pressure, cardiac index, peak positive and negative dp/dt than did the untreated, sham-operated rats. However, quinapril significantly improved these hemodynamic changes induced by infarction: left ventricular end-diastolic pressure, right atrial pressure, and total peripheral resistance index were significantly decreased, and cardiac index and peak negative dp/dt were significantly increased. Blood pressure reduction with quinapril was less marked under anesthesia than in conscious state (Fig. 1, Table 1). Renal surface blood flow was not affected by infarction or quinapril.

3.4. Body, heart and kidney weights

Body weight of 24-week-old SHR was similar in each group (Table 2). In the sham-operated rats, quinapril reduced heart weight resulting from the decrease of left ventricular weight. The untreated rats with infarction developed greater heart weight than did the untreated sham-operated rats. This was due to the marked increase in the right ventricular weight (116%), whereas left ventricular weight was similar in the sham- and coronary-ligated rats. Quinapril significantly decreased both right and left ventricular weight (22 and 14%, respectively) in the infarcted rats. Kidney weight was similar in the 4 groups.

4. Discussion

The present study provides first evidence that a pretreatment with quinapril in SHR with acute myocardial infarction is hemodynamically beneficial, despite a significant fall in blood pressure. This was substantiated by the fact that the mortality in the treated rats with infarction was not increased compared with the untreated counterparts.

Our SHR with infarction developed severe congestive heart failure, as evidenced by markedly elevated left ventricular end-diastolic pressure and decreased cardiac output. SHR with infarction developed more marked heart failure compared with normotensive rats (Nishikimi et al., 1995), suggesting that cardiac function of the hypertrophied heart is more compromised compared with the normal heart after infarction. Quinapril significantly improved markedly decreased cardiac performance in our SHR with infarction, a finding in accordance with a previous report (Nishikimi et al., 1995). After infarction, blood pressure was decreased significantly but the magnitude of its decrease was comparable in the treated and untreated rats. Similar results were also reported in infarcted SHR treated with a converting enzyme inhibitor, delapril (Nishikimi et al., 1995). These findings suggest that no unfavorable hypotension developed with acute angiotensin-converting inhibition even in hypertensive rats with infarction. There was some discrepancy in the blood pressure reduction with quinapril measured under anesthesia and in conscious state: the former being less marked than the latter. This may be due to the difference of blood pressure measurement or the effect of anesthesia.

Heart rate tended to be lower in our untreated rats with infarction compared with the sham-operated counterparts, a finding at variance with previous reports in which heart rate was either increased (Fletcher et al., 1982) or unchanged (Nishikimi et al., 1995) in infarcted SHR. Although the reason for this discrepancy is unknown, the difference of anesthesia (pentobarbital vs. ether) or the depth of anesthesia (pentobarbital 30 vs. 50 mg/kg) may explain it. The treated rats with infarction had significantly higher heart rate compared with the untreated infarcted rats. This is most likely due to lower heart rate in the latter. Reflex tachycardia is unlikely because heart rate in the treated rats with infarction was actually normalized.

In contrast to previous reports, our rats with infarction had similar left ventricular weight compared with the sham-operated rats (Fletcher et al., 1982; Nishikimi et al., 1995). After infarction, myocardial hypertrophy develops at non-infarcted areas in the left ventricle, probably due to the activated renin–angiotensin system and pressure and volume overload. The combination of the loss of myocytes at infarct site and myocardial hypertrophy at non-infarcted area would have resulted in no increase in left ventricular weight in our rats with infarction. On the other hand, right ventricular weight in the infarcted rats was greater than in the sham-operated rats, as reported by others (Fletcher et al., 1982; Nishikimi et al., 1995). Interestingly, SHR with infarction developed more significant right ventricular hypertrophy compared with normotensive counterparts (Fletcher et al., 1982; Nishikimi et al., 1995). Right ventricular hypertrophy results from pulmonary hypertension secondary to heart failure (Fletcher et al., 1982; Pfeffer and Pfeffer, 1988). The elevated right heart pressure in the present study could be a combination of pulmonary hypertension and increased right ventricular preload. Activated cardiac renin–angiotensin system may also contribute to right ventricular hypertrophy (Hirsch et al., 1991). Quinapril decreased ventricular hypertrophy and dilatation significantly in the infarcted SHR. Similar results were reported with lisinopril in normotensive rats with infarction (Mulder et al., 1997). This may be due to the suppression of the activated cardiac renin–angiotensin system, in addition to the reduction of pressure and volume overload. The reversal of cardiac hypertrophy and dilatation is beneficial for cardiac performance after infarction (Nishikimi et al., 1995; Pfeffer and Pfeffer, 1988).

However, some human and animal studies have shown that the angiotensin-converting enzyme inhibitors administered immediately after myocardial infarction decreased cardiac function (Schoemaker et al., 1991) and did not improve mortality (Swedberg et al., 1992). Inappropriate hypotension and/or disturbance of cardiac remodeling are implicated to explain the unfavorable effects. Although the exact mechanisms regarding the discrepancy between the present and these previous studies are not clear, the most important and yet unresolved issue would be timing and dosage. Deleterious effects are reported only when angiotensin-converting enzyme inhibition was started within 24 h of infarction (Swedberg et al., 1992; Schoemaker et al., 1991). After infarction, rapid activation of the renin–angiotensin system develops (Brilla et al., 1995; Hirsch et al., 1991). The acute angiotensin-converting enzyme inhibition of the activated renin–angiotensin system may cause abrupt suppression of angiotensin II production. This may result in the harmful effects, particularly acute hypotension which is common at the first dosage of angiotensin-converting enzyme inhibitors. However, if the angiotensin-converting enzyme inhibition is already present before infarction, the rapid activation of the renin–angiotensin system may be attenuated, preventing inappropriate hypotension and subsequent cardiac dilatation, as shown in this study. In agreement with our results, Stauss et al. (1994) reported beneficial effects of angiotensin-converting enzyme inhibition started 1 week before infarction in normotensive rats. These data indicate that angiotensin-converting enzyme inhibitors initiated before infarction exert hemodynamically beneficial effects in normotensive as well as in hypertensive rats.

For the treatment of congestive heart failure, relatively low doses of angiotensin-converting enzyme inhibitors are commonly used. Recent studies, however, recommend high doses (Nussberger et al., 1994; SAVE Investigators, 1992). The greatest degree of angiotensin-converting enzyme inhibition and lowest plasma angiotensin II levels in patients with congestive heart failure were observed with the highest dose of quinapril (Nussberger et al., 1994). In view of these data, we employed a large dose of quinapril used in SHR before (Albaladejo et al., 1994). Despite a significant fall of blood pressure, there were no adverse effects even in the acute phase of infarction in our SHR.

5. Conclusion

Our study indicates that a prior treatment with a depressor dosage of quinapril in SHR was beneficial for cardiac function and cardiac remodeling (decreased ventricular hypertrophy and dilatation) after acute myocardial infarction. This is of clinical importance because angiotensin-converting enzyme inhibitors are often used for hypertensive patients with left ventricular hypertrophy and some of them may develop acute myocardial infarction.

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