Reversal of Early Metabolic Dysfunction in Hypertensive Rat Left-Ventricular Myocytes by Angiotensin-Converting Enzyme Inhibition

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SUMMARY

We evaluated the effects of angiotensin-converting enzyme (ACE) inhibition on metabolic changes in myocardial organelles, myocardial hypertrophy, and interstitial fibrosis in the early stage of hypertension. An ACE inhibitor, imidapril (2.5 mg/kg per day), a calcium-channel blocker, diltiazem (30 mg/kg per day), or vehicle was given to spontaneously hypertensive rats (SHRs) from 10 to 18 weeks of age. Single myocytes were isolated enzymatically from the left ventricles of these SHRs and normotensive Wistar-Kyoto (WKY) controls at 18 weeks of age. In single ventricular myocytes, enzyme activities in the sarcoplasmic reticulum (SR) and the sarcolemma (SL) and the mitochondrial respiratory control ratio (RCR) were determined. In 18-week-old SHRs receiving vehicle, myocardial hypertrophy and interstitial fibrosis developed, and SR Ca\(^{2+}\) ATPase activity and the mitochondrial RCR were significantly lower and SL Na\(^+\), K\(^+\)-ATPase activity was significantly higher than in age-matched WKYs. However, compared with diltiazem, imidapril was better able to prevent the development of myocardial hypertrophy and interstitial fibrosis, to improve SR Ca\(^{2+}\)-ATPase activity and the mitochondrial RCR, and to increase SL Na\(^+\), K\(^+\)-ATPase activity. These results suggest that ACE inhibition can prevent the development of morphologic changes associated with hypertension-induced left ventricular remodeling, such as myocardial hypertrophy and interstitial fibrosis, and can counteract ongoing dysfunction of organelle metabolism early in the development of hypertension. (Jpn Heart J 1997; 38: 503-514)

Key words: Angiotensin-converting enzyme inhibition, Calcium-channel blockade, Spontaneously hypertensive rat heart, Left ventricular remodeling, Single ventricular myocytes, Metabolic dysfunction of organelles

HYPERTENSION, along with myocardial infarction, diabetes, valvular heart disease, and the cardiomyopathies, is a cardinal risk factor for congestive heart failure. Recently, the appropriate treatment of mild hyperten-
sion has been considered from the viewpoint of long-term prognosis. Although numerous antihypertensive drugs are now available, calcium-channel blockers and angiotensin-converting enzyme (ACE) inhibitors are most widely used. Calcium-channel blockers were initially developed for treatment of ischemic heart disease and also are now used for control of hypertension. ACE inhibitors have been the subject of numerous studies in both animals and humans. In addition to having antihypertensive effects, ACE inhibitors reverse structural changes in myocardium associated with remodeling. Although these beneficial effects of ACE inhibitors have been studied extensively, little is known about the effects on metabolic changes in myocardial organelles.

In this study, we used single myocytes isolated from the left ventricle of spontaneously hypertensive rats (SHRs), which are widely regarded as the best animal model of human genetic hypertension, to exclude any neuronal or hormonal influences and investigated structural and metabolic changes in myocardial organelles early in the development of hypertension. We also evaluated the cardioreparative effect of ACE inhibitors on these changes and their antihypertensive effect compared with those of calcium-channel blockers in single left ventricular myocytes of SHRs.

**MATERIALS AND METHODS**

**Animal experiment:** Forty 10-week-old male SHRs were used in this study. At this age, hypertension is regarded to be at an early stage of development. Twenty 10-week-old male normotensive Wistar-Kyoto rats (WKYs) served as controls. First, 10 SHRs and 10 WKYs were sacrificed at 10 weeks of age to investigate hypertension-induced left ventricular remodeling and metabolic changes in myocardial organelles. The remaining 30 SHRs were randomly divided into three groups of 10 animals, which received imidapril, an ACE inhibitor, 2.5 mg/kg per day; diltiazem, a calcium-channel blocker, 30 mg/kg per day; or vehicle only. The remaining 10 WKYs received the same vehicle. Drugs and vehicle were administered orally via a stomach tube daily from 10 weeks of age for 8 weeks. The three groups of SHRs and the WKYs were sacrificed at 18 weeks of age to evaluate the effects of the drugs on left ventricular remodeling and metabolic changes in myocardial organelles. Blood pressure was measured in all animals at 10 and 18 weeks of age with the standard tail-cuff method.

**Isolation of single ventricular myocytes:** Left ventricular myocytes were obtained by enzymatic digestion of hearts according to the method of Tytgat. Rats were anesthetized with sodium pentobarbital (70 mg/kg, i.p.) and kept in the supine position for about 10 minutes. Blood was obtained from the abdominal aorta to measure plasma renin activity and angiotensin II. The heart was
excised quickly, placed in ice-cold oxygenated saline, and weighed. The heart was cannulated via the aorta and perfused retrogradely with oxygenated Krebs-Henseleit solution containing 118 mM NaCl, 25 mM NaHCO₃, 4.7 mM KCl, 2.5 mM CaCl₂, 1.2 mM MgSO₄, 1.2 mM KH₂PO₄, 0.5 mM Na₂EDTA, and 11 mM glucose at pH 7.4 with a Langendorff perfusion apparatus for 10 minutes at 37°C to wash out all residual blood. After the heart began to beat regularly again, it was perfused with a basic solution containing Joklik minimum essential medium (Gibco, Grand Island, NY, USA), 60 mM taurine, 20 mM creatine, and 5 mM HEPES at pH 7.4 which caused the heart to stop beating. Perfusion continued for 5 minutes with the basic solution supplemented with 7000 units collagenase (Worthington, Freehold, NJ, USA) and 12 μM CaCl₂. Next, the cannula was removed, and the heart was placed in a Petri dish. The left ventricle was dissected, chopped coarsely, and shaken for 10 minutes in the basic solution supplemented with 2000 units collagenase (Worthington, Freehold, NJ), 1.5% bovine serum albumin (BSA) fraction V (Sigma, St. Louis, MO, USA), and 50 μM CaCl₂ at 37°C. The isolated-cell suspension was filtered through a nylon mesh to eliminate large superfluous cellular material and washed twice with the basic solution supplemented with 1.0% BSA. The yield was determined by cell count, and cells were considered viable when they appeared rod-shaped on light microscopy. This method routinely produced 70% to 80% fresh, rod-shaped cells. Aliquots of the isolated-cell suspension were treated with saponin (Sigma, St. Louis, MO) for 2 minutes to produce permeabilized ventricular myocytes. After the cells had settled, the supernatant was gently discarded with a pipette to wash out saponin and replaced with a cytosolic solution containing 20 mM NaCl, 100 mM KCl, 5 mM MgSO₄, 0.96 mM NaH₂PO₄, 1 mM EGTA, 5 mM HEPES, and 1.0% BSA at pH 7.2 and room temperature.

Biochemical analysis: The Ca²⁺-ATPase activity of the sarcoplasmic reticulum (SR), the Ca²⁺-ATPase activity and the Na⁺, K⁺-ATPase activity of the sarcolemma (SL), and the respiratory activity of mitochondria were determined with permeabilized ventricular myocytes. The SR Ca²⁺-ATPase activity was measured according to the modified method of Harigaya and Schwartz. Myocytes (5 × 10⁵) were incubated with 0.1 mM CaCl₂ and 0.08 mM GEDTA, or with 1.0 mM GEDTA alone at 37°C in a solution containing 100 mM KCl, 5 mM MgCl₂, 5 mM Na₃, 5 mM ATP, and 20 mM TES-Tris at pH 7.2 for 6 minutes. Liberated inorganic phosphorus was measured by the modified method of Fiske and Subbarow. The activity of SR Ca²⁺-ATPase was expressed as the difference in the amounts of Ca²⁺ and GEDTA.

The SL Ca²⁺-ATPase activity was measured by the modified method of
Myocytes \((5 \times 10^5)\) were incubated with or without \(3 \mu M\) vanadate at \(37^\circ C\) in a solution containing \(0.1 mM CaCl_2, 0.08 mM GEDTA, 160 mM KCl, 5 mM MgCl_2, 5 mM ATP,\) and \(20 mM TES-Tris\) at pH 7.4 for 6 minutes. Liberated inorganic phosphorus was measured by the same method.\(^1\) The activity of SL Ca\(^{2+}\)-ATPase was expressed as the difference in the activity inhibited by vanadate.

The SL Na\(^+\), K\(^+\)-ATPase activity was measured by the modified method of Matsuoka.\(^1\) Myocytes \((5 \times 10^5)\) were incubated with or without \(1 mM\) ouabain at \(37^\circ C\) in a solution containing \(100 mM NaCl, 10 mM KCl, 5 mM MgCl_2, 50 mM histidine,\) and \(5 mM ATP\) at pH 7.4 for 6 minutes, and liberated inorganic phosphorus was measured by the same method.\(^1\) The activity of SL Na\(^+\), K\(^+\)-ATPase was expressed as the difference in the activity inhibited by ouabain.

Mitochondrial respiratory activity was measured with an oxygen electrode (Do meter TD-650, Toko, Tokyo) according to the method of Konno and Kako.\(^1\) The reduction of oxygen concentration was determined polarographically in the cytosolic solution supplemented with succinate as a substrate and 0.625 mM ADP. Respiration states III and IV and the respiratory control ratio (RCR, state III/state IV) were calculated according to the method of Chance and Williams.\(^1\)

**Histologic observation:** Myocardium was obtained from the free wall, septum, and apex of the left ventricle in each group. Myocardial transverse diameters were measured with myocardium strained with hematoxylin-eosin, and areas occupied by interstitial fibrosis stained with Mallory's Azan were evaluated semiquantitatively by the point count method using a light microscope. Furthermore, myocardium was obtained from the same areas for ultrastructural observation. Myocardium was prefixed with a solution containing \(2.0%\) glutaraldehyde and \(0.1 M Na-cacodylate\) at pH 7.4 for 2 hours at \(0^\circ C;\) rinsed with \(0.1 M cacodylate\) and sucrose; and fixed with \(1.0% OsO_4.\) Fixed specimens were dehydrated, embedded in Epon 812, and sectioned into \(1-\mu m\) slices with a ultramicrotome (Sorvall MT-2, Dupont, USA). Sections were double-stained and observed with an electron microscope (Hitachi H-300, Tokyo, Japan).

**Data analysis:** Results are expressed as mean \(\pm\) SD. Statistical evaluation of the data was performed using Student's \(t\)-test for unpaired observations. When more than two groups were compared, ANOVA was used. Differences were considered statistically significant at \(p < 0.05.\)

**RESULTS**

**Body weight and heart weight:** Body weight and heart weight were significantly lower in untreated SHRs than in WKYs (both \(p < 0.05\)) at 10 weeks of age.
Table I. General Characteristics of Wistar-Kyoto Rats and Spontaneously Hypertensive Rats

<table>
<thead>
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<th>10 weeks of age</th>
<th>18 weeks of age</th>
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<tr>
<td></td>
<td>WKY</td>
<td>SHR</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>295 ± 38</td>
<td>264 ± 30*</td>
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<tr>
<td>Heart weight (g)</td>
<td>1.11 ± 0.20</td>
<td>1.09 ± 0.13*</td>
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<tr>
<td>Heart wt/body wt (mg/g)</td>
<td>3.75 ± 0.54</td>
<td>4.10 ± 0.54</td>
</tr>
<tr>
<td>PRA (ng/ml/hour)</td>
<td>10.4 ± 6.2</td>
<td>12.8 ± 4.6</td>
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<tr>
<td>Angiotensin II (pg/ml)</td>
<td>2.92 ± 0.93</td>
<td>24.6 ± 11.0*</td>
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</table>

WKY = Wistar-Kyoto rats; SHR = spontaneously hypertensive rats; IML = imidapril-treated SHR; DTZ = diltiazem-treated SHR; Vehicle = vehicle-treated SHR; PRA = plasma renin activity; wt = weight. *p < 0.05 versus 10-week-old WKY; †p < 0.05 versus vehicle-treated SHR; ‡p < 0.01 versus vehicle-treated SHR.

At 18 weeks of age, body weight did not differ significantly among vehicle-treated SHRs, imidapril-treated SHRs, diltiazem-treated SHRs, and WKYs. Heart weight was significantly lower in imidapril-treated SHRs (p < 0.01) and diltiazem-treated SHRs (p < 0.05) than vehicle-treated SHRs. The heart-to-body weight ratio did not differ significantly between untreated SHRs and WKYs at 10 weeks of age and became significantly greater in vehicle-treated SHRs than in WKYs (p < 0.05) at 18 weeks of age. However, the ratio was significantly lower in imidapril-treated SHRs and diltiazem-treated SHRs than in vehicle-treated SHRs (both p < 0.05) at 18 weeks of age.

**Blood pressure:** The difference in systolic blood pressure between untreated SHRs (170 ± 22 mm Hg) and WKYs (90 ± 12 mm Hg) was significant (p < 0.01) at 10 weeks of age, and became even greater (220 ± 44 mm Hg vs. 110 ± 20 mm Hg, p < 0.01) between vehicle-treated SHRs and WKYs at 18 weeks of age. Systolic blood pressure was significantly lower (p < 0.01) in both imidapril-treated SHRs (130 ± 20 mm Hg) and diltiazem-treated SHRs (120 ± 16 mm Hg) than in vehicle-treated SHRs. However, the difference in systolic blood pressure between the two drug-treated groups was not significant.

**Plasma renin activity and plasma angiotensin II:** Plasma renin activity did not differ significantly between untreated SHRs and WKYs at 10 weeks of age or among vehicle-treated, imidapril-treated, diltiazem-treated SHRs, and WKYs at 18 weeks of age (Table I). The difference in plasma angiotensin II between untreated SHRs and WKYs was significant (p < 0.05) at 10 weeks of age and became even greater (p < 0.01) between vehicle-treated SHRs and WKYs at 18 weeks of age. However, plasma angiotensin II was significantly lower in imidapril-treated SHRs than in vehicle-treated SHRs (p < 0.05) but did not differ significantly between diltiazem-treated SHRs and vehicle-treated SHRs.

**Histologic changes in myocardium:** Myocardial transverse diameter (p < 0.01) and areas occupied by interstitial fibrosis (p < 0.001) were significantly greater in untreated SHRs than in WKYs at 10 weeks of age (Table II). Further-
Table II. Myocardial Hypertrophy and Interstitial Fibrosis

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<th>10 weeks of age</th>
<th>18 weeks of age</th>
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<tbody>
<tr>
<td></td>
<td>WKY</td>
<td>SHR</td>
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<tr>
<td>Myocardial transverse diameter (µm)</td>
<td>10.8 ± 1.2</td>
<td>12.8 ± 1.3*</td>
</tr>
<tr>
<td>Areas occupied by interstitial fibrosis (%)</td>
<td>9.6 ± 1.4</td>
<td>12.8 ± 1.7†</td>
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WKY = Wistar-Kyoto rats; SHR = spontaneously hypertensive rats; IML = imidapril-treated SHR; DTZ = diltiazem-treated SHR; Vehicle = vehicle-treated SHR. *p < 0.01 versus 10-week-old WKY, †p < 0.001 versus 10-week-old WKY, ‡p < 0.01 versus vehicle-treated SHR, §p < 0.001 versus vehicle-treated SHR.

Figure 1. Ultrastructural observation of myocardium. Bars show 1 µM. A: In vehicle-treated SHRs at 18 weeks of age, as shown in the center, several mitochondria were slightly swollen and some cristae were disrupted. B: In imidapril-treated SHRs at 18 weeks of age, these changes tended to be decreased.

more, myocardial transverse diameter and areas occupied by interstitial fibrosis were significantly greater (both p < 0.001) in vehicle-treated SHRs than in WKYs at 18 weeks of age. However, myocardial transverse diameter (p < 0.01) and areas occupied by interstitial fibrosis (p < 0.001) were significantly lower in imidapril-treated SHRs than in vehicle-treated SHRs but did not differ significantly between diltiazem-treated SHRs and vehicle-treated SHRs.

On ultrastructural observation of myocardium, differences between untreated SHRs and WKYs did not differ markedly at 10 weeks of age. However, several mitochondria were slightly swollen and some cristae were disrupted only in vehicle-treated SHRs at 18 weeks of age (Figure 1). Only imidapril tended to decrease these changes in myocardial organelles.

SR Ca²⁺-ATPase activity: The SR Ca²⁺-ATPase activity was significantly lower in untreated SHRs than in WKYs (46.9 ± 9.3 vs. 60.8 ± 4.5 p moles Pi/cell/hour, p < 0.05) at 10 weeks of age (Figure 2). This difference between vehicle-treated SHRs and WKYs became even greater (40.5 ± 1.4 vs. 56.7 ± 1.2 p moles...
Pi/cell/hour, $p < 0.01$) at 18 weeks of age. However, the activity was significantly higher ($p < 0.01$) in both imidapril-treated SHRs (54.2 ± 9.9 p moles Pi/cell/hour) and diltiazem-treated SHRs (50.8 ± 9.2 p moles Pi/cell/hour) than in vehicle-treated SHRs but did not differ significantly between imidapril-treated SHRs and diltiazem-treated SHRs.

**SL Ca²⁺-ATPase activity:** The SL Ca²⁺-ATPase activity did not differ between untreated SHRs (5.1 ± 2.3 p moles Pi/cell/hour) and WKYs (5.8 ± 2.0 p moles Pi/cell/hour) at 10 weeks of age and between vehicle-treated SHRs (4.0 ± 1.4 p moles Pi/cell/hour) and WKYs (5.3 ± 2.3 p moles Pi/cell/hour) at 18 weeks of age (Figure 3). The SL Ca²⁺-ATPase activity improved significantly more only in imidapril-treated SHRs (6.6 ± 3.6 p moles Pi/cell/hour, $p < 0.05$) than in vehicle-treated SHRs but did not differ significantly between diltiazem-treated SHRs (4.9 ± 3.4 p moles Pi/cell/hour) and vehicle-treated SHRs.
**SL Na⁺, K⁺-ATPase activity:**  The SL Na⁺, K⁺-ATPase activity was significantly higher in untreated SHRs than in WKYs (15.0 ± 1.9 vs. 6.6 ± 4.0 p moles Pi/cell/hour, \( p < 0.05 \)) at 10 weeks of age (Figure 4). The difference between vehicle-treated SHRs and WKYs became even greater (16.8 ± 2.1 vs. 6.3 ± 2.9 p moles Pi/cell/hour, \( p < 0.01 \)) at 18 weeks of age. The SL Na⁺, K⁺-ATPase activity was significantly higher in imidapril-treated SHRs (25.1 ± 3.9 p moles Pi/cell/hour, \( p < 0.05 \)) but was significantly lower in diltiazem-treated SHRs (6.6 ± 3.2 p moles Pi/cell/hour, \( p < 0.01 \)) than in vehicle-treated SHRs.

**Mitochondrial RCR:** The mitochondrial RCR did not differ significantly between untreated SHRs and WKYs (3.3 ± 1.3 vs. 4.0 ± 0.7, NS) at 10 weeks of age and was significantly lower in vehicle-treated SHRs than in WKYs (2.5 ± 1.1 vs.
3.5 ± 1.7, *p < 0.05*) at 18 weeks of age (Figure 5). The mitochondrial RCR improved significantly more only in imidapril-treated SHRs than in vehicle-treated SHRs (3.1 ± 0.9 vs. 2.5 ± 1.1, *p < 0.05*) but did not differ significantly between diltiazem-treated SHRs (2.7 ± 1.2) and vehicle-treated SHRs.

**DISCUSSION**

Blood pressure is significantly higher in SHRs than WKYs at 5 weeks of age and increases further only in SHRs by about 5 to 10 weeks of age.²¹ We investigated metabolic changes in organelles of the SHR heart at 10 weeks, when hypertension is regarded to be at an early stage of development. We found that mitochondrial respiratory activity and SL Ca²⁺-ATPase activity were maintained at 10 weeks, that SR Ca²⁺-ATPase activity had significantly decreased, and that SL Na⁺, K⁺-ATPase activity had significantly increased.

**SR Ca²⁺-ATPase activity:** According to the study of Komuro et al.,²² SR Ca²⁺-ATPase gene expression is suppressed and SR Ca²⁺-ATPase activity decreases when pressure overload induces cardiac hypertrophy in hypertensive Wistar rats. In our study, SR Ca²⁺-ATPase activity decreased from the early stage of hypertension in a similar manner. The ability to take up Ca²⁺ into the SR in diastole also decreased, which increased the free Ca²⁺ concentration in diastole. We surmise that an insufficient decrease in the intracellular Ca²⁺ concentration in diastole is partly responsible for the disturbance of diastolic function. Furthermore, a decrease in Ca²⁺ storage in the SR depresses Ca²⁺ release from the terminal cisterna of the SR in systole, which eventually leads to contraction failure.

**SL Na⁺, K⁺-ATPase activity:** Previous reports have not reached a consensus regarding Na⁺, K⁺-ATPase activity in the SHR heart.²³⁻²⁵ An increase in Na⁺, K⁺-ATPase gene expression is observed with Northern blot analysis in the SHR heart at 4 weeks of age, i.e., before the development of hypertension. Godfraind et al.²⁷ and David-Dufilho et al.²⁸ report that the Na⁺, K⁺-ATPase activity is increased in SHRs aged 3 weeks and 7 weeks, respectively, which are before the development of hypertension. These findings agree with those of the present study. Torii et al.²⁹ also report that the Na⁺, K⁺-ATPase activity of the SHR heart is increased at 6 weeks of age, which is before the development of hypertension, and at 10 weeks of age, which is early in the development of hypertension, and is decreased at 16 weeks of age. We speculate that an increase in the intracellular Ca²⁺ concentration caused by dysfunction of SR Ca²⁺-ATPase might accelerate the Na⁺, Ca²⁺ exchange system. Consequently, Na⁺ might be incorporated in the myocyte and SL Na⁺, K⁺-ATPase activity might increase to compensate for the increase in intracellular Na⁺.³⁰

**Differences in effects of ACE inhibition and calcium-channel blockade:**
Left ventricular hypertrophy and the metabolic changes in organelles of the SHR heart stated above were observed early in the development of hypertension and then tended to progress with age. The heart weight and the heart-to-body weight ratio could be reduced and the depressed activity of SR Ca\(^{2+}\)-ATPase associated with pressure overload could be reversed by administration of an ACE inhibitor, imidapril, and a calcium-channel blocker, diltiazem. The reversal of hypertension-induced cardiac hypertrophy and dysfunction of SR Ca\(^{2+}\)-ATPase activity may be related to the antihypertensive effects of both drugs. Diltiazem has the beneficial effects of preventing left ventricular hypertrophy, preserving left ventricular function,\(^{31}\) and protecting SR Ca\(^{2+}\)-ATPase activity against ischemic injury.\(^{32}\)

Imidapril significantly reduced plasma levels of angiotensin II and prevented the development of myocardial hypertrophy and interstitial fibrosis. In contrast, the effects of diltiazem were not significant. ACE inhibitors can decrease volume overload by inhibiting the renin-angiotensin system and, by inhibiting the local production of angiotensin II in the heart, can suppress the development of myocardial hypertrophy and interstitial fibrosis.\(^{33,34}\) The recently introduced angiotensin II receptor antagonists, losartan and TCV-116, can provide similar benefits.\(^{35,36}\) Blockade of the renin-angiotensin system is thought to be important in the prevention of the development of left ventricular remodeling as well as in the prevention of hypertension. In this study, imidapril restored the activities of SL Ca\(^{2+}\)-ATPase and mitochondrial respiration significantly more than did diltiazem. Imidapril had greater beneficial effects on hypertension-induced myocardial hypertrophy, interstitial fibrosis, and metabolic dysfunction of myocardial organelles than did diltiazem despite a lack of difference in antihypertensive effect.\(^{37}\) ACE inhibitors might be more beneficial than calcium-channel blockers for reversing hypertension-induced structural and metabolic changes in myocardium.

Diltiazem normalized SL Na\(^{+}\)-K\(^{+}\) ATPase activity of SHRs to that of WKY controls. In contrast, imidapril significantly increased SL Na\(^{+}\), K\(^{+}\)-ATPase activity, thereby altering the ionic environment of myocytes. However, whether an increase in SL Na\(^{+}\), K\(^{+}\)-ATPase activity induced by ACE inhibition benefits the heart is still controversial. Our hypothesis for the mechanism by which SL Na\(^{+}\), K\(^{+}\)-ATPase activity is increased is described below. Inhibition of ACE suppresses not only the production of angiotensin II but also the breakdown of bradykinin.\(^{38,39}\) In the heart, local bradykinin might activate the Na\(^{+}\), H\(^{+}\) exchange system\(^{40}\) and, consequently, Na\(^{+}\) might be incorporated in the myocyte. The Na\(^{+}\), K\(^{+}\) ATPase activity might then be increased to compensate for the increase in intracellular Na\(^{+}\).

**Conclusion:** Inhibition of ACE could prevent the development of morphologic
changes associated with hypertension-induced left ventricular remodeling, such as myocardial hypertrophy and interstitial fibrosis, and could reverse ongoing dysfunction of organelle metabolism early in the development of hypertension.

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**REFERENCES**

27. Godfraind T, Noel F. Sodium activation of heart (Na\textsuperscript{+}-K\textsuperscript{+})-ATPase from normotensive and spontaneously hypertensive rats. Arch Int Pharmacodyn 1980; 215: 139–44.