Altered Inotropic Responsiveness and Gene Expression of Hypertrophied Myocardium With Captopril


Abstract—Inotropic responsiveness to β-adrenergic stimulation is generally found to be impaired in left ventricular (LV) hypertrophy and failure. To investigate the mechanisms by which angiotensin-converting enzyme inhibitor therapy may modulate inotropic responsiveness with long-term pressure overload, we studied the effects of captopril treatment on cardiac gene expression, LV muscle mechanical contraction, and intracellular calcium (Ca\(^{2+}\)) transients from spontaneously hypertensive rats (SHR). LV papillary muscles from untreated SHR, age-matched normotensive Wistar-Kyoto rats (WKY), and SHR treated with captopril (CAPRx started at 12, 18, and 21 months of age) were studied. All animals were studied at 24 months of age or when heart failure developed. In untreated SHR, α-myosin heavy chain (MHC) gene expression and protein were decreased, the Ca\(^{2+}\) transient (with the bioluminescent indicator aequorin) was prolonged, and abundance of Na\(^+\)/Ca\(^{2+}\) exchanger mRNA levels increased in comparison to WKY. Active stress development at L\(_{\text{max}}\) and the maximum rate of stress development were depressed and contractile duration prolonged in SHR relative to WKY. Isoproterenol administration further decreased active stress in untreated SHR despite an increase in intracellular Ca\(^{2+}\) levels. In CAPRx SHR, α-MHC gene expression and protein levels were increased, the Ca\(^{2+}\) transient was not prolonged, Na\(^+\)/Ca\(^{2+}\) exchanger expression was downregulated, and papillary muscle function demonstrated increased active stress and maximum rate of stress development in response to isoproterenol. The increased abundance of α-MHC mRNA in conjunction with an increase in V\(_1\) myosin isozyme suggests that captopril affects transcriptional regulation of cardiac gene expression. Restored LV inotropic responsiveness to β-adrenergic stimulation in CAPRx SHR appears to be coupled to normalization of Na\(^+\)/Ca\(^{2+}\) exchanger mRNA expression, upregulation of V\(_1\) myosin isozyme levels, and increased speed of contraction. (Hypertension. 2000;35:1203-1209.)

Key Words: hypertrophy, left ventricular ■ heart failure ■ calcium ■ receptors, adrenergic, beta

Decreased myocardial responsiveness to β-adrenergic stimulation with hypertrophy\(^1,2\) and failure\(^3,4\) has been primarily attributed to changes in the β-adrenergic receptor. However, in the spontaneously hypertensive rat (SHR), a polygenic model of long-term pressure overload--induced hypertrophy and failure, no decrease in β-adrenergic receptor density or affinity was found,\(^5\) suggesting that other factors also may modulate sensitivity. Downregulation of α-myosin heavy chain (α-MHC) with a concomitant upregulation of β-MHC has been observed in murine species during myocardial hypertrophy and failure.\(^6\)\(^,\)\(^7\) Until recently, this was not believed to be an important factor in the regulation of myocardial contractility in human myocardium, but recent observations in failing human myocardium indicate that systolic dysfunction was associated with a downregulation of α-MHC\(^8\)\(^,\)\(^9\) and upregulation of Na\(^+\)/Ca\(^{2+}\) exchanger gene expression.\(^10\)\(^,\)\(^11\) A close relation between α-MHC and β-adrenergic receptor gene expression was found, and it has been suggested that these 2 genes may be coregulated.\(^9\) We have recently demonstrated that treatment with the angiotensin-converting enzyme (ACE) inhibitor captopril causes a progressive upregulation of α-MHC gene expression in the SHR and prevents the transition to failure.\(^12\) Although there is generally a parallel relation between expression of mRNA for α-MHC and β-MHC and protein production, a recent report in aortic banded rats\(^13\) indicates a dissociation between gene expression and protein levels. Therefore, it is important to determine the effects of ACE inhibitor on both expression of mRNA coding for α-MHC and on protein production.

In the present study, we examined the relation between the time ACE inhibitor treatment is initiated and its effects on isoproterenol (ISO)-mediated changes in inotropic responsiveness and intracellular calcium ([Ca\(^{2+}\)]\(_i\)) and to quantify changes in α-MHC gene expression and protein and Na\(^+\)/Ca\(^{2+}\) exchanger gene expression and protein. The presence of heart failure significantly decreased myocardial responsiveness to β-adrenergic stimulation in SHR. α-MHC gene expression and protein levels were increased, the Ca\(^{2+}\) transient was not prolonged, Na\(^+\)/Ca\(^{2+}\) exchanger expression was downregulated, and papillary muscle function demonstrated increased active stress and maximum rate of stress development in response to isoproterenol. The increased abundance of α-MHC mRNA in conjunction with an increase in V\(_1\) myosin isozyme suggests that captopril affects transcriptional regulation of cardiac gene expression. Restored LV inotropic responsiveness to β-adrenergic stimulation in CAPRx SHR appears to be coupled to normalization of Na\(^+\)/Ca\(^{2+}\) exchanger mRNA expression, upregulation of V\(_1\) myosin isozyme levels, and increased speed of contraction.
exchanger mRNA with long-term ACE inhibition in hypertrophied and failing myocardium from the SHR.

Methods

Animal Model
Forty-three male SHR and 12 Wistar-Kyoto rats (WKY) were purchased from Taconic. Rats were housed 2 per cage and fed standard rat chow and allowed free access to water. Captopril was added to drinking water at a concentration of 2 g/L (CAPRx), which has been shown to be effective in preventing hemodynamic impairment associated with chronic hypertrophy in the SHR. Groups of SHR had CAPRx initiated at 12, 18, and 24 months of age (SHR-Rx18, SHR-Rx21, and SHR-Rx24, respectively). Control groups included untreated age-matched SHR and WKY and 12-month CAPRx-treated WKY. Animals were monitored with measurements of body weight and blood pressure (peak systolic arterial blood pressure was measured in the conscious animals by the tail-cuff method). Animals were also observed for evidence of tachypnea and labored respiration; when these findings became evident, animals were killed and blood pressure (peak systolic arterial blood pressure was determined and averaged and force normalized for muscle cross-sectional area. There were no significant differences in muscle stress). At Lmax, isometric contraction parameters of 5 twitches were considered significant at P<0.05. Peak systolic arterial pressure was higher in untreated SHR before CAPRx and decreased with CAPRx but remained higher than WKY.

Aequorin Studies
Aequorin was loaded into the muscle preparations by the macrinojection technique as previously described. After loading, muscles were allowed to equilibrate for 90 to 120 minutes until a steady state was achieved. Light and force signals were recorded and analyzed by a digital recording system developed in our laboratory. The fractional luminescence method was used to provide calibration for comparison of light signals among groups.

Experimental Protocol
After aequorin loading and equilibration, muscle preparations were exposed to concentrations of Ca2+ (0.6, 1.2, 2.5, and 5 mmol/L) for 10 minutes each, a period during which active force stabilized. The muscles were then allowed to reequilibrate at the baseline Ca2+ concentration (1.2 mmol/L) for 30 minutes before the addition of ISO (10^-4, 10^-3, and 10^-2 mol/L) to the bath at 10-minute intervals. At 10^-8 mol/L ISO, the Ca2+ in the bath was increased to 2.5 and then 5 mmol/L. The muscle bath was then drained and washed with normal Krebs solution and changed to 1.25 mmol/L Ca2+ and equilibrated for 30 minutes before calcium calibration.

Tissue Isolation and Preparation
After removal of the papillary muscles, the heart was dissected into atria, LV, and right ventricles (RV). Tissues were gently blotted and weighed. LV samples were quickly frozen and stored in liquid nitrogen. LV and RV weight-normalized by body weight were used as indexes of ventricular hypertrophy.

Myosin Isozyme Studies
The methods for tissue preparation, myosin extraction, and electrophoretic separation of isomyosins have been previously described. Briefly, myosin was extracted from ~200 mg of the frozen LV. Isomyosins were separated by electrophoresis on polyacrylamide gels, under nondissociating conditions as described by Hoh et al. The gels were fixed, stained with Coomassie blue R 250, then scanned on a Joyce Loebl scanning densitometer at 520 nm. The relative proportions of the isomyosins present were obtained from the gels by measuring the area under each peak to obtain a final estimate of the proportion of V1 (heavy chain-α) and V2 (heavy chain-β) isomyosins present.

Analysis of Cardiac Na+/Ca2+ Exchanger and α-MHC mRNA Levels
Frozen samples of LV tissue were processed and the RNA extracted for Northern blot analysis of Na+/Ca2+ exchanger and α-MHC mRNA expression as previously published. Briefly, RNA was isolated from cardiac tissue by the method of Chomczynski and Sacchi. Ten micrograms of total RNA was size-fractionated by electrophoresis and transferred to nylon membranes (Genescreen Plus; Dupont NEN). A rat cDNA for Na+/Ca2+ exchanger was labeled with 32p-5'-dCTP using random hexamer priming and hybridized to nylon blots for 18 to 24 hours at 42°C. Probes for α-MHC and 18S ribosomal RNA were end-labeled synthetic oligonucleotides previously described. Washed blots were exposed to film, and the signals were quantified by a densitometric system (GS700, BioRad). Blots were probed with a 32p-labeled oligonucleotide complementary to 18S ribosomal RNA. Levels of mRNA reported here are normalized to the level of 18S rRNA.

Statistical Analysis
Data from the SHR-F, SHR-NF, and WKY groups were compared with the use of 1-way ANOVA with replication. A 2-way ANOVA was used to examine group and treatment effects. The Newman-Keuls multiple-sample comparison test or Tukey's procedure was used to localize differences where appropriate. Differences were considered significant at P<0.05. Data are expressed as mean±SD.

Results

Animal Weights, LV Weight, Heart Chamber Ratios, and Blood Pressure Changes
CAPRx decreases cardiac hypertrophy, as indicated by decreases in LV/body weight (BW) and RV/BW in comparison to untreated SHR (Table 1). In CAPRx, SHR RV/BW was not significantly different from the WKY, whereas LV/BW was elevated relative to untreated WKY (P<0.05). Peak systolic arterial pressure was higher in untreated SHR before CAPRx and decreased with CAPRx but remained higher than WKY.

Intracellular Calcium Transient and Isometric Stress Recordings
Examples of light and force signals from untreated WKY, SHR-NF and SHR-F, and CAPRx SHR (SHR-Rx18) at 1.25 mmol/L Ca2+ ([Ca2+]i) bath, in response to 10^-6 mol/L ISO and the addition of 5 mmol/L Ca2+ in the presence of ISO, are presented in Figure 1. Before ISO, peak σ was depressed in SHR relative to WKY and SHR-NF. WKY demonstrated a parallel increase in + dσ/dt and [Ca2+]i, in response to ISO. In contrast, muscles from untreated SHR-NF and SHR-F rats demonstrate a decrease in peak σ and + dσ/dt in response to ISO despite an increase in peak [Ca2+]i. In
untreated WKY, superimposed recording of peak σ demonstrates a further positive inotropic response to subsequent addition of 5 mM/L Ca\(^{2+}\) to the bath in the presence of ISO (10\(^{-6}\) mol/L). The ISO plus 5 mM/L Ca\(^{2+}\) increased peak σ and +dσ/dt above control (1.2 mM/L Ca\(^{2+}\)) levels in the WKY, whereas in the untreated SHR groups, elevated Ca\(^{2+}\) bath fails to restore peak σ to pre-ISO levels despite a marked increase in the amplitude of the Ca\(^{2+}\) signal. In SHR-F, increasing the [Ca\(^{2+}\)]\(_{o}\) bath to 5 mM/L in the presence of ISO (10\(^{-6}\) mol/L) caused a late rises in the diastolic Ca\(^{2+}\) signal (Figure 1). CAPRx SHR demonstrate positive inotropy (peak σ and +dσ/dt) in response to ISO, which is further increased with ISO plus 5 mM/L Ca\(^{2+}\).

There were no significant differences in peak systolic intracellular [Ca\(^{2+}\)], or resting [Ca\(^{2+}\)], (0.2 to 0.3 μmol/L range) among groups. The duration of the [Ca\(^{2+}\)] signal and TPσ was prolonged in the SHR relative to WKY (Table 2). In SHR, CAPRx decreased TPσ and duration of the light signal when treatment was initiated at 12 months of age and to a lesser extent at 18 and 21 months. TPL and RL\(_{1/2}\) were significantly abbreviated with CAPRx (SHR-NF and SHR-F versus SHR-Rx\(_{12}\)).

There was no significant difference in TPσ or TPL+RL\(_{1/2}\) between WKY and SHR-Rx\(_{12}\); −dQ/dt/Q was found to be slower in untreated SHR relative to WKY. This index of Ca\(^{2+}\) sequestration became progressively higher (faster) in SHR with CAPRx initiated at 21, 18, and 12 months of age.

**Response to β-Adrenergic Stimulation**

The relative changes in peak σ, +dσ/dt, and [Ca\(^{2+}\)], with increasing ISO bath expressed as a percentage of control at 1.2 mM/L [Ca\(^{2+}\)], bath from untreated WKY, SHR-NF, and SHR-F are presented in Figure 2 (top; CAPRx SHR shown at bottom). In WKY, peak [Ca\(^{2+}\)], and +dσ/dt increased with ISO, whereas peak σ at L\(_{max}\) was only slightly increased and TPσ decreased. In SHR-NF and SHR-F, despite an increase in [Ca\(^{2+}\)], peak σ and +dσ/dt fell in response to ISO, whereas TPσ decreased (P<0.05 SHR-NF and SHR-F versus WKY). In contrast, in SHR-Rx\(_{12}\), ISO increased peak σ and peak +dσ/dt, whereas TPσ decreased (NS SHR-Rx\(_{12}\) versus WKY). CAPRx of SHR starting at 21 months of age resulted in a small increase in +dσ/dt, whereas peak σ and TPσ deceased slightly.

**Response to Calcium**

The response of peak σ, +dσ/dt, and [Ca\(^{2+}\)], with increasing [Ca\(^{2+}\)], bath in untreated WKY, SHR-NF, and SHR-F (top) and CAPRx SHR groups (bottom) is presented in Figure 3. Peak σ, +dσ/dt, and the Ca\(^{2+}\) signal peak increased in all groups with and without CAPRx, when the [Ca\(^{2+}\)], of the bath was increased from 0.6 to 5.0 mM/L, whereas TPσ and TPL+RL\(_{1/2}\) did not change.

**Na\(^{+}/Ca\(^{2+}\)** Exchanger Expression

Figure 4 (left) shows representative autoradiogram of Na\(^{+}/Ca\(^{2+}\) exchanger mRNA as detected by Northern hybridization from the LV of WKY, SHR-NF, and SHR-F. There was an increased abundance of Na\(^{+}/Ca\(^{2+}\) exchanger mRNA of the LV from SHR-NF and marked increase in the SHR-F in comparison to age-matched WKY (P<0.05). CAPRx reduced

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**TABLE 1. Body Weight, Cardiac Chamber Weight, Chamber Weight–to–Body Weight Ratios, and In Vivo Systolic Blood Pressure**

<table>
<thead>
<tr>
<th></th>
<th>BW, g</th>
<th>LV/BW, mg/g</th>
<th>RV/BW, mg/g</th>
<th>LV wt, g</th>
<th>RV wt, g</th>
<th>Blood Pressure, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>WKY (n=9)</td>
<td>639±132</td>
<td>1.88±0.26</td>
<td>0.48±0.04</td>
<td>1.18±0.16</td>
<td>0.30±0.04</td>
<td>118±9 113±4</td>
</tr>
<tr>
<td>SHR (n=15)</td>
<td>358±55†</td>
<td>3.84±0.44†</td>
<td>0.91±0.13†</td>
<td>1.35±0.15</td>
<td>0.33±0.06</td>
<td>180±6 158±8†</td>
</tr>
<tr>
<td>SHR-Rx (n=28)</td>
<td>387±26‡</td>
<td>2.54±0.38‡</td>
<td>0.59±0.08‡</td>
<td>0.98±0.14</td>
<td>0.23±0.05</td>
<td>190±146 144±106§</td>
</tr>
</tbody>
</table>

WKY indicates normotensive WKY; SHR, all spontaneously hypertensive rats. All CAPRx SHR combined with treatment initiated at 12, 18, and 21 months of age and all animals studied at 24 months of age (SHR-Rx). Blood Pressure indicates peak systolic blood pressure before study at 12 months of age (Pre) and at time of study 21 to 24 months of age (Post). Values are mean±SD. *P<0.05, †P<0.01 SHR vs WKY, ‡P<0.05 SHR-Rx vs SHR, §P<0.05, SHR-Rx vs WKY.

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**Figure 1.** Examples of Ca\(^{2+}\) transients and peak σ from papillary muscles in response to ISO (10\(^{-6}\) mol/L) and ISO plus 5 mM/L Ca\(^{2+}\) from normotensive WKY rats (top), untreated SHR (SHR-NF; middle), and failing SHR (SHR-F; third from top) and CAPRx SHR for 12 months (SHR-Rx\(_{12}\); bottom). Response to 1.2 mM/L Ca\(^{2+}\) before ISO is presented for comparison (1.2); Light responses are presented on left and peak σ on right.
LV was greatest in the 12-month CAP Rx group and increased myocardial inotropic responsiveness to ISO, in association with reversal of changes in α-MHC and Na\(^+\)/Ca\(^{2+}\) exchanger gene expression, in the SHR during the transition to failure. Impaired responsiveness to β-adrenergic stimulation is one of the earliest changes reported with myocardial hypertrophy\(^1,2,24\) and failure.\(^3,4,25,26\) Recent observations in failing human myocardium indicate that systolic dysfunction was associated with a downregulation of α-MHC\(^6,9\) and upregulation of Na\(^+\)/Ca\(^{2+}\) exchanger gene expression.\(^10,11\)

In acute myocardial infarction and aortic banding models, ISO induces a blunted but nevertheless positive inotropic response,\(^27-29\) whereas in the SHR with long-standing hypertrophy, ISO decreases isometric force at Lmax. ACE inhibition has been shown to partially improve responsiveness to ISO in the infarcted\(^27\) but not the aortic-banded myocardium.\(^28\) In the present study, 3 to 12 months of CAP Rx restored the positive inotropic responsiveness of the SHR myocardium to ISO. Previous studies have noted impaired inotropic responsiveness of hypertrophied myocardium to ISO without β-adrenergic receptor changes.\(^2\) Our laboratory has demonstrated a depressed inotropic response of LV papillary muscles from hypertrophied and failing SHR hearts to ISO but not Ca\(^{2+}\) (Reference 16), despite an increase in LV

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### Table 2. Characteristics of Papillary Muscle Function and Intracellular Calcium

<table>
<thead>
<tr>
<th></th>
<th>No. PM</th>
<th>α Active</th>
<th>TPα</th>
<th>Peak [Ca(^{2+})]</th>
<th>TPL + RL(^{1/2})</th>
<th>−[dQ/dt]/Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>WKY</td>
<td>8</td>
<td>3.2 ± 0.7</td>
<td>146 ± 10</td>
<td>0.87 ± 0.19</td>
<td>80 ± 14</td>
<td>45 ± 5</td>
</tr>
<tr>
<td>SHR-NF</td>
<td>6</td>
<td>3.0 ± 1.0</td>
<td>179 ± 7*</td>
<td>1.04 ± 0.23</td>
<td>114 ± 16*</td>
<td>36 ± 9</td>
</tr>
<tr>
<td>SHR-F</td>
<td>9</td>
<td>1.7 ± 0.8*</td>
<td>171 ± 13*</td>
<td>0.92 ± 0.15</td>
<td>117 ± 14*</td>
<td>35 ± 4*</td>
</tr>
<tr>
<td>SHR-Rx12</td>
<td>9</td>
<td>3.9 ± 2.3</td>
<td>169 ± 18</td>
<td>0.84 ± 0.19</td>
<td>93 ± 12</td>
<td>41 ± 3</td>
</tr>
<tr>
<td>SHR-Rx18</td>
<td>8</td>
<td>3.2 ± 1.5</td>
<td>159 ± 11</td>
<td>0.75 ± 0.11</td>
<td>80 ± 18</td>
<td>47 ± 10</td>
</tr>
<tr>
<td>SHR-Rx21</td>
<td>9</td>
<td>4.1 ± 3.0†</td>
<td>144 ± 16†</td>
<td>0.68 ± 0.13</td>
<td>71 ± 8†</td>
<td>50 ± 6†</td>
</tr>
</tbody>
</table>

WKY indicates normotensive Wistar-Kyoto rats; SHR-NF, SHR without failure; SHR-F, SHR with failure; SHR-Rx, all CAP Rx. SHR groups with treatment initiated at 12, 18 and 21 months of age and all animals studied at 24 months of age. PM, papillary muscle preparations; α Active, active stress at Lmax (g/mm²); TPα, time to peak α (ms); peak [Ca\(^{2+}\)]; peak systolic Ca\(^{2+}\) (µmol/L); TPL + RL\(^{1/2}\), time to peak and time to 50% decline in peak [Ca\(^{2+}\)]; signal; and −[dQ/dt]/Q, maximum rate of decline of the Ca\(^{2+}\) signal normalized by its peak. Values are mean ± SD. *P<0.05 vs WKY; †P<0.05 vs SHR-NF; ‡P<0.05 vs SHR-F.

### Discussion

The present study demonstrates that long-term CAP Rx restores myocardial inotropic responsiveness to ISO, in association with reversal of changes in α-MHC and Na\(^+\)/Ca\(^{2+}\) exchanger gene expression, in the SHR during the transition to failure. Impaired responsiveness to β-adrenergic stimulation is one of the earliest changes reported with myocardial hypertrophy\(^1,2,24\) and failure.\(^3,4,25,26\) Recent observations in failing human myocardium indicate that systolic dysfunction was associated with a downregulation of α-MHC\(^6,9\) and upregulation of Na\(^+\)/Ca\(^{2+}\) exchanger gene expression.\(^10,11\)

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**Figure 2.** Concentration-response of peak α, +dα/dt, and peak [Ca\(^{2+}\)], signal to increasing ISO (10⁻⁸, 10⁻⁷ and 10⁻⁶ mol/L) in WKY (○), SHR-NF (●), and SHR-F (□) (top). Effect of CAP Rx of SHR is presented on bottom. CAP Rx was initiated in SHR at 12, 18, and 21 months of age, and all animals were studied at 24 months of age. Values are expressed as percentage of values observed at 1.2 mmol/L Ca\(^{2+}\). Data are mean ± SD.

**Figure 3.** Concentration-response of peak α, +dα/dt, and peak [Ca\(^{2+}\)], to increasing Ca\(^{2+}\) (0.6, 1.2, 2.5, and 5.0 mmol/L) in WKY (○), SHR-NF (●), and SHR-F (□) (top). Top, Peak α, +dα/dt, and peak [Ca\(^{2+}\)] are expressed as percent change from values observed at 0.6 mmol/L Ca\(^{2+}\). Effect of CAP Rx on SHR is presented on bottom. Format is similar to Figure 2. Data are mean ± SD.
β-adrenergic receptor density with failure and an increase in the peak transient intracellular Ca2+. These findings suggest that depressed LV inotropic responsiveness is unlikely to be mediated by downregulation of the β-receptors and may implicate postreceptor mechanisms, such as altered Ca2+ dynamics or myofilament responsiveness.

Responsiveness of cardiac myofilaments to Ca2+ may be modulated by a change in kinetics of the actin-myosin cross-bridge turnover or may be influenced in vivo by a number of intracellular effectors, including pH and cAMP; the effects of these factors on V1 and V3 myosin may differ. In CAP-Rx SHR, the relative proportion of V1 myosin isozyme present was associated with improved inotropic responsiveness to ISO. Epinephrine has been shown to increase cross-bridge cycling rate in V1 to a greater extent than in V3 myosin, since cAMP does not increase myosin ATPase activity in myocardium containing V1 myosin. Depressed myocardial contractile sensitivity to catecholamines has been related to the concentration of V3 myosin isozyme. Dibutyryl cAMP, which exerts a positive inotropic effect without stimulation of the β-receptor, has also been shown to have a smaller inotropic response in LV papillary muscles compared with CAP-Rx SHR (SHR-Rx) (right). Na+/Ca2+ mRNA expression was increased in the SHR-NF and further increased in the SHR-F relative to WKY, whereas CAP-Rx of SHR decreased expression. *P<0.05, SHR-F vs WKY and SHR-Rx.

TABLE 3. Percent V1, Myosin Isozyme Composition of LV

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<tr>
<th>Treatment</th>
<th>No. of LV Samples</th>
<th>% V1</th>
</tr>
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<tbody>
<tr>
<td>Untreated</td>
<td>8</td>
<td>24±11</td>
</tr>
<tr>
<td>SHR</td>
<td>8</td>
<td>24±11</td>
</tr>
<tr>
<td>Captopril-treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR-Rx2</td>
<td>5</td>
<td>53±26</td>
</tr>
<tr>
<td>SHR-Rx18</td>
<td>6</td>
<td>64±26*</td>
</tr>
<tr>
<td>SHR-Rx26</td>
<td>5</td>
<td>77±21*</td>
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SHR indicates all untreated SHR; SHR-Rx2, SHR-Rx18, SHR-Rx26, captopril-treated SHR with treatment initiated at 12, 18, and 21 months of age; all treated SHR studied at 24 months of age, % V1, % of myosin isozyme composition. Values are mean±SD.

*P<0.05 vs untreated SHR.

β-receptors and may affect postreceptor mechanisms, such as altered Ca2+ dynamics or myofilament responsiveness.

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<td></td>
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<tr>
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</tr>
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*P<0.05 vs untreated SHR.

β-receptors and may affect postreceptor mechanisms, such as altered Ca2+ dynamics or myofilament responsiveness.

Responsiveness of cardiac myofilaments to Ca2+ may be modulated by a change in kinetics of the actin-myosin cross-bridge turnover or may be influenced in vivo by a number of intracellular effectors, including pH and cAMP; the effects of these factors on V1 and V3 myosin may differ. In CAP-Rx SHR, the relative proportion of V1 myosin isozyme present was associated with improved inotropic responsiveness to ISO. Epinephrine has been shown to increase cross-bridge cycling rate in V1 to a greater extent than in V3 myosin, since cAMP does not increase myosin ATPase activity in myocardium containing V1 myosin. Depressed myocardial contractile sensitivity to catecholamines has been related to the concentration of V3 myosin isozyme. Dibutyryl cAMP, which exerts a positive inotropic effect without stimulation of the β-receptor, has also been shown to have a smaller inotropic response in LV papillary muscles compared with CAP-Rx SHR (SHR-Rx) (right). Na+/Ca2+ mRNA expression was increased in the SHR-NF and further increased in the SHR-F relative to WKY, whereas CAP-Rx of SHR decreased expression. *P<0.05, SHR-F vs WKY and SHR-Rx.

TABLE 3. Percent V1, Myosin Isozyme Composition of LV

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of LV Samples</th>
<th>% V1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>8</td>
<td>24±11</td>
</tr>
<tr>
<td>SHR</td>
<td>8</td>
<td>24±11</td>
</tr>
<tr>
<td>Captopril-treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR-Rx2</td>
<td>5</td>
<td>53±26</td>
</tr>
<tr>
<td>SHR-Rx18</td>
<td>6</td>
<td>64±26*</td>
</tr>
<tr>
<td>SHR-Rx26</td>
<td>5</td>
<td>77±21*</td>
</tr>
</tbody>
</table>

SHR indicates all untreated SHR; SHR-Rx2, SHR-Rx18, SHR-Rx26, captopril-treated SHR with treatment initiated at 12, 18, and 21 months of age; all treated SHR studied at 24 months of age, % V1, % of myosin isozyme composition. Values are mean±SD.

*P<0.05 vs untreated SHR.
CAMP, and myosin shifts, findings not seen in compensated SHR treated with captopril, suggest that several factors may be required for the positive inotropic response to catecholamines and may contribute to contractile depression seen with failure. Because both calcium handling and downstream myofilament responsiveness are affected, the present results demonstrate that captopril can modulate transcriptional regulation of expression of multiple cardiac genes to reverse hypertrophic changes that effect contractility and enhance myocardial β-adrenergic responsiveness.

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References


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