Impaired Skeletal Muscle Performance in the Early Stage of Cardiac Pressure Overload in Rabbits: Beneficial Effects of Angiotensin-Converting Enzyme Inhibition

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ABSTRACT

Abnormalities of skeletal muscles are frequently observed in patients with congestive heart failure. In these patients, angiotensin-converting enzyme (ACE) inhibitors improve exercise performance. The present study was designed to assess whether skeletal muscle dysfunction develops in the early stage of cardiac overload and if so, whether such functional alterations can be prevented by ACE inhibition. Mechanical performance, cross-bridge (CB) properties, and myosin heavy chain composition were investigated in respiratory and limb skeletal muscles of rabbits with moderate cardiac hypertrophy, and after single therapy with the ACE inhibitor perindopril (PE). After constriction of the aorta, the rabbits were treated during a 10-week period with either PE (1 mg/kg/day; n = 9) or a placebo (PL; n = 15). A third group of sham-operated animals received PL (n = 10). Analyses were performed on isolated diaphragm and soleus strips. Compared with sham-operated animals (shams), peak tetanic tension in PL fell by 40% in diaphragm and 34% in soleus. There were no significant differences in peak tetanic tension and the maximum shortening velocity between PE and shams. In both muscles, the total number of CBs was significantly lower in PL than in shams, but did not differ between shams and PE. The elementary force per CB did not differ between groups. In both muscles, the myosin heavy chain composition did not differ between groups. The study demonstrated that intrinsic performance of diaphragm and soleus muscles was affected early in the development of chronic pressure overload. Single therapy with PE tended to preserve muscle strength, essentially by limiting the loss of CBs.

Numerous studies have reported respiratory muscle weakness during chronic congestive heart failure in both humans (De Troyer et al., 1980; Hammond et al., 1990; Mancini et al., 1992; McParland et al., 1992) and animals (Supinski et al., 1994; Howell et al., 1995; Lecarpentier et al., 1998). This weakness, likely due to structural (Sullivan et al., 1990; Lindsay et al., 1996; Tikunov et al., 1997), metabolic (Weiner et al., 1986; Mancini et al., 1989; Wilson et al., 1992), and biochemical changes (Massie et al., 1988; Sullivan et al., 1990; Drexler et al., 1992), may contribute, at least in part, to exercise intolerance and excessive ventilatory response. Alterations in limb skeletal muscle metabolism have also been reported in experimental cardiac volume overload without congestive heart failure (Chati et al., 1994), raising the possibility that reduced intrinsic muscle performance may develop in the early stage of heart failure.

Effective therapies to improve prognosis and exercise tolerance have been established for chronic heart failure. Angiotensin-converting enzyme (ACE) inhibitors prolong life (The SOLVD Investigators, 1991) and also improve skeletal muscle flow and peak oxygen consumption during exercise (Mancini et al., 1987; Drexler et al., 1992) in patients with chronic heart failure. Peripheral improvements are associated with a gradual reversal of chronic structural alterations in skeletal muscle (Drexler et al., 1992; Schaufelberger et al., 1996). Whether these effects are associated with improved intrinsic muscle performance and whether beneficial effects are observed at an early stage of cardiac hypertrophy remain to be determined.

In the present study, skeletal muscle performance was studied in a rabbit model of chronic cardiac hypertrophy before the occurrence of congestive heart failure (CHF). The

ABBREVIATIONS: ACE, angiotensin-converting enzyme; PL, placebo; PE, perindopril; Lo, optimal initial muscle length; Po, maximum isometric tension; CB, cross-bridge; CHF, congestive heart failure; MHC, myosin heavy chain.
first aim of the study was to determine to what extent intrinsic diaphragm weakness occurred in early stages of pressure cardiac overload. Given that cardiac diseases may not affect respiratory and limb skeletal muscles in the same way (Hammond et al., 1990; Howell et al., 1995; Tikunov et al., 1997), we also examined the intrinsic performance of soleus muscle. The second aim of our study was to determine whether a preventive therapy with the ACE inhibitor perindopril (PE) had any beneficial effects on intrinsic skeletal muscle performance during moderate pressure cardiac overload. The third aim was to determine whether modifications in molecular cross-bridge (CB) properties were involved in the potential changes in skeletal muscles during chronic cardiac overload.

We therefore investigated the number, kinetics, and single force of CBs (Lecarpentier et al., 1997, 1998; Coirault et al., 1997) and the MHC composition of diaphragm and soleus muscles.

**Materials and Methods**

**Preparation of Animals and Surgical Procedure.** Animal care conformed to international guidelines. Surgical procedures were performed after induction and maintenance of anesthesia with midazolam (0.5 mg, i.v.) and etomidate (4.5 mg, then 20 mg/h, i.v.). Subtotal constriction of the suprarenal abdominal aorta was carried out on female adult New Zealand rabbits. The abdominal aorta was surgically isolated just below the diaphragm and a piece of polyethylene catheter (external diameter of 2.4 mm; Biotrol, Paris) was positioned along it. The catheter and the aorta were ligated together just above the right renal artery and then the catheter was gently removed. This procedure reduced the abdominal aortic lumen by 45% (Gilsoul et al., 1990). This model constantly induces moderate cardiac hypertrophy with preserved systolic function. Thereafter, the rabbits were randomly treated by p.o. gavage with either PE (1 mg/kg/day; n = 9) or a placebo (PL; n = 15). A third group of sham-operated animals received PL (n = 10). Sham-operated animals were subjected to the same operation without inducement of aortic constriction. Treatment was administered 7 days a week for 10 weeks.

**Mounting Procedure and Mechanical Analysis.** After anesthesia with sodium pentobarbital (30 mg/kg, i.p.), the animals were thoracotomized and then laparotomized. Two muscle strips were carefully excised per animal from the ventral part of the costal diaphragm. A strip was also dissected from the soleus muscle. Each muscle strip was rapidly mounted in a tissue chamber containing a Krebs-Henseleit solution: 118 mmol/l NaCl, 24 mmol/l NaHCO3, 4.7 mmol/l KCl, 1.2 mmol/l MgSO4·7H2O, 1.1 mmol/l KH2PO4, 2.5 mmol/l CaCl2·6H2O, and 4.5 mmol/l glucose. The solution was bubbled with a gas mixture of 95% O2-5% CO2 and maintained at 22°C and pH 7.4. Tendinous extremities were held in spring clips and attached to an electromagnetic force transducer. The electromagnetic lever system used has been described previously (Lecarpentier et al., 1997). Muscles were electrically stimulated by means of two platinum electrodes delivering 1-ms rectangular pulses at 0.17 Hz. Experiments were carried out at the optimal initial resting length (Lo), which corresponds to the apex of the length-active tension curve. The muscle cross-sectional area (in mm2) was calculated from the ratio of fresh muscle weight to muscle length at Lo.

**Study Protocol.** Tension-frequency curves were determined by stimulating muscle strips at 25, 33, 50, 75, 100, 200, and 400 Hz (train duration: 400 ms, 10/min). The peak isometric tension; i.e., peak force normalized per cross-sectional area, was measured from the fully isometric contraction. Tension-frequency relationships were expressed in terms of absolute tension (in mN · mm⁻²) and of percentage of maximum isometric tension (Po) at the optimal tetanic frequency.

Thereafter, mechanical experiments were performed at the optimal tetanic frequency. The peak velocity (V) of 8 to 10 contractions was plotted against the isotonic load level normalized per cross-sectional area (P), obtained by successive load increments from zero-load up to the isometric tension. Maximum unloaded shortening velocity (Vmax, in Lo · s⁻¹) was measured from the contraction abruptly clamped to zero-load just after stimulus. The experimental P-V relationship was fitted according to Hill’s equation (Hill, 1964): (P + a) (V + b) = (cPmax + a₂b), where a and b are the asymptotes of the hyperbola and cPmax is the calculated peak isometric tension for V = 0. The curvature G of the P-V relationship is equal to (cPmax/b² = (cPmax/a)², where cPmax is the calculated peak velocity at zero-load.

### CB Number and Kinetics.

According to the most widely accepted theory of contraction (Huxley, 1957), CBs act as independent force generators. Therefore, muscle force depends on the elementary force produced per CB and the total number of CBs formed. A. F. Huxley’s equations (Huxley, 1957) were used to calculate the rate of total energy release (E, in mW · mm⁻²), the isotonic tension (Pmax, in mN · mm⁻²), and the rate of mechanical energy (Wh, in mW · mm⁻²) as a function of velocity (V). In these equations, f1 is the maximum value of the rate constant for CB attachment and g1 and g2 are the peak values of the rate constants for CB detachment (Huxley, 1957).

The instantaneous movement x of the myosin head relative to actin varies from h to 0, where h is the step size of the CB; h is defined by the translocation distance of the actin filament per ATP hydrolysis and produced by the swing of the myosin head (Huxley, 1969); f1 and g1 correspond to x = h, and g2 corresponds to x = h (Huxley, 1957); s is the resting sarcomere length at Lo; 12 h = h (Huxley, 1957); for reasons of equation dimensions, h is multiplied by s/2 compared with the initial hypothesis (Huxley, 1957). Consequently, calculations of f1, g1, and g2 were divided by s/2 compared with those previously detailed (Lecarpentier et al., 1997, 1998; Coirault et al., 1997) and are given by the following equations:

\[
\begin{align*}
\ell = & \frac{-g_1 + \sqrt{g_1^2 + 4g_2g_2}}{2} \\
\ell = & \frac{2V_{\text{max}}}{g_1} \\
W = & \frac{2wb}{ehG}
\end{align*}
\]

where w is the mechanical work of a single CB, and e is the free energy required to split one ATP molecule (Huxley 1969; Eisenberg et al., 1990, Huxley and Simmons, 1971).

The minimum value of the rate of total energy release (E₀, in mW · mm⁻²) occurs in isometric conditions; E₀ is equal to the product of a × h (Huxley, 1957; Woldege et al., 1985) and is also given by the equation:

\[
E_0 = (ms/2)e \frac{h}{2f_1g_1}
\]

where m/s is the CB number per mm² at peak isometric tension and \( \ell \) is the distance between two actin sites. The maximum turnover rate of myosin ATPase per site in isometric conditions (k_max, in s⁻¹) is E₀/(ema/2) (Huxley, 1957). The total duration of the time cycle is tc = 1/k_max.

The elementary force per single CB in isometric conditions II, in piconewtons (pN) is:

\[
II = P_{\text{flux max}}/(ms/2) = \frac{w}{\ell f_1 + g_1}
\]

The rate of mechanical work \( W_M \) is

\[
W_M = P_{\text{flux}} \cdot V
\]

At any given load level, the mechanical efficiency (Eff) of the muscle is defined as the ratio of \( W_M/E \) (Huxley, 1957):

\[
\text{Eff} = \frac{W_M}{E} = \text{Eff}_{\text{max}}
\]
The accuracy and reliability of A.F. Huxley’s parameters depend on how well the experimental data can be fitted to Huxley’s equations. The validity of each of the mathematical fits was checked as previously reported (Lecarpentier et al., 1998).

**Values of Huxley’s Equation Constants.** A stroke size of 11 nm has been determined by means of optical tweezers (Finer et al., 1994) and corresponds to the three-dimensional structure of the myosin head (Rayment et al., 1993). The distance \( \ell \) is equal to 36 nm (Woledge et al., 1985). The free energy required to split one ATP molecule per contraction site is \( 3.8 \times 10^{-20} \) J. The mechanical work \( (w) \) of a single CB is equal to 0.75 e (Huxley, 1957), so that \( w = 3.8 \times 10^{-20} \) J.

**Myosin Electrophoresis.** Preparations of crude myosin were obtained from the ventral part of the costal diaphragm and from soleus muscles, as previously described (Coirault et al., 1997). Electrophoresis was performed in a Bio-Rad Mini-Protein II Dual Slab Cell electrophoresis system (Bio-Rad, Hercules, CA) for 24 h at 4°C and 70 V (constant voltage). MHCS were separated in dissociating conditions with 0.75 mmol SDS-polyacrylamide gel minigel electrophoresis (Talmage and Roy, 1993; Mortola and Naso, 1995). Stacking gel was composed of 4% acrylamide (2.67% bis-acrylamide), 70 mmol Tris (pH 6.8), 30% glycerol, 4 mmol EDTA, and 0.1% SDS. The composition of separating gel was 8% acrylamide (1% bis-acrylamide), 0.2 mol Tris pH 8.8, 0.1 mol glycine, and 0.4% SDS. Separate upper and lower running buffers were used. The upper running buffer consisted of 0.1 mol Tris (base), 150 mmol glycine, and 0.05% SDS. The lower running buffer consisted of 50 mmol Tris (base), 75 mmol glycine, and 0.05% SDS. Both buffers were prepared shortly before use and cooled at 4°C. Gels were stained with 0.2% Coomassie blue, 50% ethanol, and 10% acetic acid, and destained with 5% ethanol and 5% acetic acid. The different MHCS isoforms were quantified by one-dimensional densitometry (GS-690; BioRad). The amount of each isoform was determined by the area of each peak.

**Data Analysis.** The areas of all peaks were summed. Data were expressed as percentages of the area of each peak over the sum of the areas of all peaks.

**Plasma ACE Assay.** Blood samples were taken after catheterization of the right ventricle. The samples were centrifuged for 10 min at 10,000xg at 4°C, and plasma was stored at −80°C. The tripeptide (14C)-hippuric acid generated was extracted with ethanol and 5% acetic acid. The different MHC isoforms were quantified by one-dimensional densitometry (GS-690; BioRad). The amount of each isoform was determined by the area of each peak over the sum of the areas of all peaks.

**Statistical Analysis.** Data are expressed as means ± S.E. Comparison of several means was performed using ANOVA and the Scheffé test. Linear regression was based on the least-squares method. The asymptotes \( a \) and \( b \) of the Hill hyperbola were calculated by means of multilinear regression and the least-squares method. A \( p \) value of <0.05 was considered statistically significant.

**Results.**

**Cardiac Hypertrophy.** In both PE and PL groups, there were no physical signs of CHF (i.e., s.c. edema, ascites, pericarditis, pleurisy, and/or pulmonary and hepatic congestion). The degree of cardiac hypertrophy was assessed in terms of the heart weight/body weight ratio. This ratio was increased by approximately 27% in PL compared with shams \( (p < .05) \) but did not differ significantly between PE and sham-operated rabbits (Table 1).

**Plasma ACE Activity.** In PE-treated rabbits, plasma ACE activity was 3.8 ± 0.8 mU/ml. Plasma ACE activity was inhibited by 95%, compared with placebo-treated rabbits (71.4 ± 5.9 mU/ml), and was inhibited by 93%, compared with shams (56.6 ± 5.9 mU/ml).

**Diaphragm Contractile Properties.** When absolute values of tension were considered at different tetanic frequencies, diaphragm strength was significantly reduced in PL, with the entire tension-frequency curve of PL shifted downward, compared with shams (Fig. 1A). However, the overall shape of tension-frequency curves were similar in shams and PL, as shown by the fact that when tension was expressed as a percentage of Po, tension-frequency curves for shams and PL groups were similar (Fig. 1B). Finally, there was no significant difference between shams and PE with regard to the tension-frequency curves.

At 33 Hz, i.e., the optimal tetanic stimulation frequency, Po, was about 40% lower in PL than in shams \( (p < .01; \) Fig. 2A). The \( V_{max} \) was also significantly lower in PL than in shams \( (p < .01; \) Fig. 2B). At the CB level, there was a significant decrease in the total number of CBs \( (10^7/m^3) \) in PL, compared with shams \( (p < .01; \) Fig. 3A). Conversely, the single force of CBs \( (F) \) did not differ between the three groups (Fig. 3B). Perindopril treatment played a significant role in preventing the decrease in Po, \( V_{max} \), and m (Figs. 2 and 3). In shams, the G curvature of the force–velocity relationship was 5.8 ± 0.7 and did not differ significantly between groups \( (5.1 ± 0.3 \text{ and } 5.5 ± 0.3 \text{ in PL and PE, respectively}) \). The maximum mechanical efficiency \( (E_{f,max}) \) was not significantly modified in PL and PE groups \( (40 ± 1 \text{ and } 41 ± \)...

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**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>PL</th>
<th>PE</th>
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<tbody>
<tr>
<td>Body weight, kg</td>
<td>3.62 ± 0.08</td>
<td>3.80 ± 0.09</td>
<td>3.35 ± 0.12**</td>
</tr>
<tr>
<td>Heart weight, g</td>
<td>7.22 ± 0.27</td>
<td>9.48 ± 0.67**</td>
<td>7.52 ± 0.36</td>
</tr>
<tr>
<td>Heart weight/body weight, g/kg</td>
<td>1.99 ± 0.06</td>
<td>2.53 ± 0.17**</td>
<td>2.26 ± 0.11</td>
</tr>
</tbody>
</table>

* \( p < .05 \), shams versus PL.
** \( p < .05 \), PL versus PE.

---

**Fig. 1.** Effects of increasing stimulation frequency on tension development in diaphragm and soleus muscles at 22°C. A, absolute peak isometric tension normalized per cross-sectional area. B, relative peak isometric tension. Values are means ± S.E.
1% in PL and PE, respectively) compared with sham values (40 ± 1%).

The rate constant for CB attachment (f₁) and detachment (g₁ and g₂) varied differently in PL and after PE treatment, compared with sham-operated animals (Table 2). Both f₁ and g₁ rate constants presented no significant differences among the three groups. The g₂ rate constant for detachment was significantly lower in PL than in shams (p < .01). PE treatment played a significant role in preventing the decrease in g₂. There was no significant difference in the total duration of the time cycle (tc) between the three groups (Table 2).

Soleus Contractile Properties. Soleus strength was significantly reduced in PL, with the entire tension-frequency curve of PL shifted downward compared with sham-operated rabbits (Fig. 1A). PE treatment tended to prevent the shift in the tension-frequency curve and no significant difference was observed between PE and shams. However, when expressed as a percentage of Po, tension-frequency curves for sham and PL groups were similar (Fig. 1B). In the three groups, Po was observed at a 33-Hz stimulation frequency (Fig. 1A). At 33 Hz, soleus Po was 33% lower and the total number of CBs was 31% lower in PL, compared with shams (p < .01 for both; Figs. 2A and 3A). Perindopril played a significant role in preventing the decrease in both Po and m (Figs. 2A and 3A).

There was no significant difference among the three groups with regard to Vmax and L (Figs. 2B and 3A). Similarly, the rate constant for attachment (f₁) and detachment (g₁ and g₂) and tc did not differ significantly among the three groups (Table 2).

MHC Distributions. Electrophoresis showed the presence of three MHC isoforms in myosin from diaphragm; namely, fast IIA and IIX and slow-type I myosin isoforms (Fig. 4). The sham soleus expressed both type I and IIA MHCs, with type I accounting for nearly 80% of the total MHC pool. In both diaphragm and soleus, there were no significant differences in MHC isoforms among the three groups (Table 3).

Discussion

We analyzed the intrinsic function of diaphragm and soleus muscles in a rabbit model of moderate cardiac hypertrophy induced by chronic pressure overload. The major findings of our study were as follows: 1) moderate cardiac hypertrophy was associated with a marked impairment in the intrinsic

### Table 2

<table>
<thead>
<tr>
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<th>f₁</th>
<th>g₁</th>
<th>g₂</th>
<th>tc</th>
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<tbody>
<tr>
<td>Diaphragm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td>68 ± 7</td>
<td>15 ± 3</td>
<td>424 ± 23</td>
<td>999 ± 253</td>
</tr>
<tr>
<td>PL</td>
<td>54 ± 3</td>
<td>12 ± 1</td>
<td>329 ± 19*</td>
<td>911 ± 131</td>
</tr>
<tr>
<td>PE</td>
<td>64 ± 4</td>
<td>12 ± 1</td>
<td>430 ± 19**</td>
<td>812 ± 104</td>
</tr>
<tr>
<td>Soleus</td>
<td></td>
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<td></td>
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<tr>
<td>Sham</td>
<td>22 ± 2</td>
<td>3 ± 1</td>
<td>194 ± 12</td>
<td>3245 ± 503</td>
</tr>
<tr>
<td>PL</td>
<td>20 ± 1</td>
<td>3 ± 1</td>
<td>177 ± 12</td>
<td>3676 ± 598</td>
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<tr>
<td>PE</td>
<td>21 ± 2</td>
<td>3 ± 1</td>
<td>190 ± 16</td>
<td>3618 ± 534</td>
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* p < .01; sham versus PL.
** p < .01; PL versus PE.
performance of diaphragm and limb skeletal muscles, at a stage when CHF has not yet occurred; 2) single therapy with the ACE inhibitor PE tended to preserve the intrinsic performance of both diaphragm and limb skeletal muscles.

**Skeletal Muscle Failure in Placebo-Treated Cardiac Hypertrophic Rabbits.** There is evidence that exercise intolerance and fatigue poorly correlate with the degree of left ventricular dysfunction (Franciosa et al., 1981; Szlachcic et al., 1985; Massie et al., 1988) and inadequate skeletal muscle blood flow (Massie et al., 1988). However, observations reported so far support the view that alterations in skeletal muscle in heart failure are, after all, the consequences of impaired cardiac function. For the first time, our results showed that rabbits with moderate cardiac hypertrophy exhibited a marked reduction in diaphragm and soleus muscle performance, indicating that skeletal muscle weakness can occur early in the course of the cardiopathy, i.e., when CHF has not yet occurred. In both PL diaphragm and soleus, lower peak tetanic tensions were associated with a significant decrease in the number of CBs.

The reduction in diaphragm strength has been found to vary from 40% (Supinski et al., 1994; Lecarpentier et al., 1998) to 60% (Howell et al., 1995) depending on the experimental model of cardiac overload. Interestingly, the almost 40% drop in diaphragm tension observed in the present study did not strikingly differ from that found in rabbit with major CHF, where heart weight/body weight ratio is increased by 165% (Lecarpentier et al., 1998). This further supports the hypothesis that intrinsic skeletal muscle weakness does not correlate with the degree of cardiac dysfunction (Franciosa et al., 1981; Szlachcic et al., 1985; Massie et al., 1988). However, several differences must be emphasized regarding skeletal muscle abnormalities during heart disease. In rabbits with major CHF caused by combined pressure and volume overload, both the number and single force of CBs account for the reduction in diaphragm tension (Lecarpentier et al., 1998), whereas no changes in the single force of CBs were observed in moderate cardiac pressure overload (present study). Changes in CB kinetics and energetics have also been previously reported in rabbits with major CHF (Lecarpentier et al., 1998). In our study, the moderate hypertrophic cardiac process was not associated with modifications in the kinetics of myosin molecular motors (except for diaphragm g2 values), nor in peak mechanical efficiency. In addition, recent studies during CHF have provided evidence of abnormal expression of myosin isoforms, suggestive of fiber type transformation and regeneration (Howell et al., 1995; Lindsay et al., 1996; Tikunov et al., 1997). In our study, the hypertrophic cardiac process was not associated with modifications in the MHC composition of diaphragm and soleus muscles. It is thus possible that the degree and/or the duration of cardiac dysfunction may influence structural and biochemical damages to skeletal muscles.

There is evidence that CHF affects respiratory and limb skeletal muscles differently (Hammond et al., 1990; McParland et al., 1992; Howell et al., 1995). Our results showed that diaphragm muscle function was weakened to a greater extent than soleus, as attested by a greater reduction in peak tension. These findings are consistent with those reported previously in patients (Hammond et al., 1990; McParland et al., 1992) and in experimental models of CHF (Howell et al., 1995). Moreover, we found that maximum shortening velocity was depressed in diaphragm from PL-treated rabbits but not in soleus. In regard to the fiber type distribution, diaphragm adapts to cardiac overload in a manner opposite to that of limb muscles (Howell et al., 1995; Tikunov et al., 1997). The cause of the structural and functional differences between respiratory and nonrespiratory muscles during cardiopathies remains unknown. One potential explanation is that changes in limb muscles may result in part from deconditioning caused by reduced physical activity, whereas diaphragm mechanical work is preserved or even increased during heart failure. Alternatively, it is tempting to speculate that disparities in regional blood flow may have different consequences, depending on the predominant fiber type in the muscle and/or the size of the muscle involved (Musch, 1993). A complex interplay between these potential contributors may explain, at least in part, the structural and functional differences between respiratory and nonrespiratory skeletal muscles.

**ACE Inhibitor Therapy.** For the first time, our study showed that early therapy with the ACE inhibitor PE tended to preserve the intrinsic performance of diaphragm and soleus muscles in rabbits with moderate cardiac hypertrophy. Previous studies have reported reversal of ultrastructural abnormalities (including reduced number and size of mitochondrial abnormalities and increased muscle fiber area and lactate dehydrogenase activity) after ACE inhibitor therapy (Drexler et al., 1992; Schaufelberger et al., 1996). In chronic cardiac pressure overload, our study indicated that preserved muscle performance after PE was mainly caused by its preventive effect on the decline in CB number. These beneficial effects of ACE could provide a partial explanation for the increased exercise capacity and higher peak oxygen consumption during exercise observed in patients suffering from CHF and receiving ACE therapy (Mancini et al., 1987; Drexler et al., 1989).

**Fig. 4.** Typical electrophoretic pattern of MHC in diaphragm and soleus from sham-operated rabbit. Homogenates prepared were subjected to SDS-glycerol electrophoresis to resolve the MHC isoforms.

**TABLE 3**

<table>
<thead>
<tr>
<th>MHC distributions in diaphragm and soleus muscles</th>
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<tr>
<td>Percentage values are mean ± S.E. Sham, n = 10; PL, n = 15; PE, n = 9. Two diaphragm and one soleus muscle strips were dissected per animal. There was no significant difference between groups.</td>
</tr>
<tr>
<td>Diaphragm</td>
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<tr>
<td>-----------</td>
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<tr>
<td>I</td>
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<td>II A</td>
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<td>II X</td>
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<td>IX</td>
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<tr>
<td>Soleus</td>
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<td>I</td>
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<td>II A</td>
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<td>II X</td>
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**ACE inhibitor PE**

[Image 44x624 to 295x729]
Whether improved skeletal muscle performance is secondary to improved hemodynamics status or whether it is a result of a direct, specific muscular effect remains to be established. Mechanical performance is highly dependent upon adequate skeletal muscle perfusion and oxygen supply. Repeated episodes of reduced blood flow within skeletal muscle during exercise have been involved in the development of skeletal muscle abnormalities (Drexler et al., 1989; Mancini et al., 1991). It has been shown that captopril therapy increases resting skeletal muscle blood flow in patients with severe CHF (Drexler et al., 1989, Thuillez et al., 1996). Reversal of the inability of peripheral vessels to dilate and/or increased capillary muscle perfusion may help preserve the intrinsic function of skeletal muscles. Alternatively, it has been established that effective therapy with PE helps to preserve the intrinsic diaphragm performance in a genetically polymyopathic model (Chemla et al., 1992; Lecarpentier et al., 1997), mainly by preventing the decrease in CBs (Lecarpentier et al., 1997). Obviously, chronic cardiac pressure overload strikingly differs from polymyopathy. These observations raised, however, the possibility that ACE inhibition may have a specific effect on ultrastructural damages and muscle dysfunction, and additional studies are needed to clarify this point.

**Conclusions.** In rabbit, chronic cardiac pressure overload without CHF induced early alterations in diaphragm and soleus muscle performance. Effective therapy with the ACE inhibitor PE tended to prevent a reduction in muscle strength and maximum shortening velocity. Changes in CB number but not in the single force per CB were the probable explanation for modifications in diaphragm and soleus strength before and after ACE therapy.

**References**


