ACE inhibition prevents myocardial infarction-induced skeletal muscle mitochondrial dysfunction

Joffrey Zoll,1,4* Laurent Monassier,2,5* Anne Garnier,3 Benoit N’Guessan,1 Bertrand Mettauer,1 Vladimir Veksler,3 François Piquard,1 Renée Ventura-Clapier,3,5 and Bernard Geny1

1Service de Physiologie et d’Explorations Fonctionnelles, EA 3072 and 2Laboratoire de Neurobiologie et de Pharmacologie Cardiovasculaire, INSERM U715, Hôpitaux Universitaires de Strasbourg, Faculté de Médecine, Strasbourg; and 3Cardiologie Cellulaire et Moléculaire U769 INSERM, Faculté de Pharmacie, Université Paris-Sud, Châtenay-Malabry, France

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Heart failure is associated with alterations in cardiac and skeletal muscle energy metabolism resulting in a generalized myopathy. We investigated the molecular and cellular effects of angiotensin-converting enzyme inhibition (ACEi) on skeletal muscle metabolism in infarcted animals. Myocardial infarction (MI) was obtained by left descending coronary artery ligation. Sham, MI, and MI-treated rats (perindopril, 2 mg · kg−1 · day−1 given 7 days after MI) were studied 1 and 4 mo after surgery. Oxygen consumption of white gastrocnemius (Gas) muscle was studied in saponin-permeabilized fibers, using the main substrates of mitochondrial respiration. mRNA expression of nuclear factors (PGC-1α, NRF-2α, and mTFA), involved in the transcription of mitochondrial proteins, and of MCIP1, a marker of calcineurin activation, were also determined. Echocardiographic left ventricular fractional shortening was reduced in both MI and perindopril group after 1 and 4 mo, whereas systemic blood pressure was reduced by 16% only in the MI group after 4 mo. The capacity of Gas to oxidize glutamate-malate, glyceral-triphosphate, or pyruvate (−30%, P < 0.01; −32%, P < 0.05; −33%, P < 0.01, respectively), was greatly decreased. Furthermore, PGC-1α (−54%), NRF-2α (−45%), and MCIP1 (−84%) gene expression were significantly downregulated. ACEi improved survival, left ventricular function, and blood pressure. Perindopril protected also totally the Gas mitochondrial function and preserved the mRNAs concentration of the mitochondrial transcriptional factors. Moreover, PGC-1α correlated with Gas oxidative capacity (r = 0.48), mitochondrial cytochrome-c oxidase (r = 0.65), citrate synthase (r = 0.45) activities, and MCIP1 expression (r = 0.44). Thus ACEi totally prevented MI-induced alterations of skeletal muscle mitochondrial function and protein expression, halting the development of this metabolic myopathy.

rehabilitation; mitochondria; angiotensin-converting enzyme inhibition

CHRONIC HEART FAILURE (CHF) is characterized by impaired cardiac function, muscular fatigue, and reduced exercise tolerance. Reduction of exercise capacities involves not only the cardiovascular system but also the skeletal muscles themselves. Indeed, clinical and animal studies described muscular atrophy associated with fiber-type phenotype shift toward a more fast-twitch glycolytic phenotype during heart failure (14, 23, 24, 26). Furthermore, impairments of mitochondrial function were observed in the heart and fast and slow skeletal muscles (3, 4) and were attributed to the downregulation of transcriptional coactivators and transcription factors implicated in mitochondrial biogenesis (PGC-1α, NRF-2α, and Tfam; Ref. 11).

The generalized character of this metabolic myopathy suggests that humoral systemic factors could be involved (27). The renin-angiotensin-aldosterone system (RAAS) is well known to be implicated in the development of peripheral abnormalities. Its key effector peptide angiotensin II, a strong vasoconstrictor augmenting vascular tone, increases left ventricular (LV) afterload, reduces cardiac and muscle perfusions, and modulates angiogenesis. Long-term angiotensin-converting enzyme inhibition (ACEi) largely improves cardiac function and remodeling in patients with heart failure and reduces systemic and local neurohormonal activations. ACEi enhances blood flow to skeletal muscle during exercise, probably in relation to peripheral (vascular) mechanisms and improved oxygen utilization (5). Accordingly, ACEi has been shown to protect cardiac muscle phenotype (12, 20), to prevent vascular alterations (17, 22), and to restore the abnormal myosin heavy chain (MHC) profile in skeletal muscle (30), in the model of myocardial infarction (MI)-induced CHF. On the other hand, ACEi failed to restore skeletal muscle’s oxidative capacity in heart failure rats secondary to aortic stenosis (16). In opposition to data obtained previously in patients without ACEi, the skeletal muscle mitochondrial function was not impaired in patients under ACEi's presenting with heart failure secondary to dilated idiopathic cardiomyopathy and ischemic heart disease (60 and 27% of the patients, respectively) in one study (15), and ischemic heart disease for 57% and dilated cardiomyopathy for 36% in another study (28). Moreover, we recently showed that preservation of skeletal muscle mitochondrial function in heart failure patients is accompanied by preserved markers and transcription factors of mitochondrial biogenesis and by calcineurin activation (9). We thus studied mRNAs coding for transcriptional coactivators and transcription factors implicated in mitochondrial biogenesis [PGC-1α, NRF-2α, and Tfam (11)], and MCIP1, a marker of calcineurin activation (31).

In view of these findings, we hypothesized that ACEi treatment could be involved in the protection of mitochondrial function through commensurate adjustments in the transcript level of mitochondrial transcription factors. The model of rat...
myocardial infarction was used because it is a clinically relevant model and because (in contrary to aortic stenosis) it allows full efficacy of ACEi.

MATERIALS AND METHODS

Animals. Male Wistar rats weighing 250 g were housed at 22 ± 2°C, on a 12:12-h photoperiod, and were provided with food and water ad libitum. This investigation was carried out in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication no. 85-23, revised 1996).

Production of the model. Under pentobarbital anesthesia (60 mg/kg), animals were intubated and artificially ventilated with room air (Ugo Basile, model 7025), and their proximal left coronary artery was ligated after left thoracotomy. Control rats were sham operated without coronary ligation.

Seven days after surgery, quantification of the MI size was performed in pentobarbital-anesthetized animals, breathing spontaneously, by two-dimensional echocardiography (Sonos 5500, Philips Ultrasound) with a 12-MHz phased array transducer (S12). Animals were divided into three groups and were analyzed 1 or 4 mo later; sham-operated untreated rats (Sham, n = 9 at 1 mo and n = 8 at 4 mo), MI untreated rats (MI, n = 9 at 1 mo and n = 8 out of 13 at 4 mo), and MI treated with perindopril (PE) (2 mg·kg⁻¹·day⁻¹ in the drinking water, MI-PE, n = 9 at 1 mo and n = 8 out of 10 at 4 mo). The treatment was administered 7 days/wk for 1 or 4 mo, the dose of PE being similar to that previously used (16). We did not study sham-operated rats treated with PE because ACEi did not modify healthy skeletal muscle mitochondrial function (1).

Cardiovascular measurements. Heart rate and systemic blood pressure were recorded 1 or 4 mo after surgery by the tail-cuff technique (LES002 storage pressure meter, Letica) in conscious rats; all data were stored in digital format (Biopac).

LV function was obtained by echocardiography 1 or 4 mo after surgery. Fractional shortening was calculated as FS = (LVEDD − LVESD/LVEDD) × 100, where LVEDD and LVESD are LV internal diameters in end-diastole and end-systole, respectively. The left ventricle score of akinesia was calculated as follows; parasternal long and short axis views were divided into four segments, and a score of 1 was given for each akinetic or dyskinetic segment or 0 if the displacement was normal. If an aneurysm was observed on a view, a score of 1 was added to this section. All measurements were obtained on at least three beats, according to the guidelines of the American Society of Echography. Only rats exhibiting significant myocardial infarction as inferred from a left ventricle score of akinesia higher than 3 were included in the study.

Tissue processing of skeletal muscle. The glycolytic superficial gastrocnemius muscle (Gas) was selected because of its higher sensitivity to heart failure (8) and because of its metabolic characteristics that make it a relevant model and because (in contrary to aortic stenosis) it allows full efficacy of ACEi.

Experimental design.

Adipose and connective tissues. Right muscle was immediately used for the study of respiratory parameters and left muscle was quickly frozen at −80°C for subsequent analysis.

Functional properties of mitochondria. The respiratory parameters of the total mitochondrial population were studied in situ in saponin-skinned fibers by a method described earlier (3). Briefly, respiratory fibers were determined by using a Clark electrode (Strathkelvin Instruments) in an oxygraphic cell at 22°C with continuous stirring. Thin muscle fibers were isolated in the skinnning (S) solution containing (in mmol/l): 2.77 CaK₂EGTA, 7.23 K₂EGTA, 6.56 MgCl₂, 5.7 Na₂ATP, 15 phosphocreatine (PCr), 20 taurine, 0.5 DTT, 50 K methanesulfonate, 20 imidazole (pH 7.1) and incubated for 30 min in solution S with 50 μg/ml saponin. Permeabilized fibers were transferred to respiration (R) solution (composition as S solution, but containing 3 mmol/l K₂HPO₄ instead of PCr and ATP) for 10 min to wash out adenine nucleotides and PCr. All steps were carried out at 4°C with continuous stirring. Respiration rates of 10−15 mg of skinned fibers were measured at 22°C in 3 ml of solution R that contained 2 mg/ml bovine serum albumin with or without substrates. After the experiment, fiber bundles were dried and weighed. Rates of respiration are given in micromoles O₂ per minute per gram dry weight. Maximal oxidative capacities were determined in the presence of ADP (2 mM), with each mitochondrial substrate added to the preparation (18, 19).

Enzyme analysis. Frozen tissue samples were weighed, homogenized into ice-cold buffer (30 mg/ml) containing (in mM) 5 HEPES, 1 EGTA, 5 MgCl₂, 1 DTT, and Triton X-100 (0.1%), pH 8.7, and incubated for 60 min at 0°C to ensure complete enzyme extraction. Citrate synthase and cytochrome-c oxidase were assessed by standard spectrophotometric methods as previously described (4).

Real-time quantitative RT-PCR analysis. Total muscle RNA was isolated from frozen tissue samples (10−20 mg) using the Trizol reagent technique. Oligo-dT first-strand cDNA was synthesized from 2 μg total RNA using Superscript II reverse transcriptase (Invitrogen). Real-time PCR was performed using the SYBRgreen technology on a LightCycler rapid thermal cycler (Roche Diagnostics) as previously described (8). The target genes were the peroxisome proliferator activated receptor gamma coactivator 1 (Pgc-1α, NM_031347, forward primer: CACCAAAACCCACAGAGACAG, reverse primer: GCAGTTCCAGAGATTTCCACA), the nuclear respiratory factor 2 (NRF-2, XM_344002, forward primer: CACCACACTCAACATTTCCG, reverse primer: CTTGGGGAC- CTTGGAACCTT), the mitochondrial transcription factor A (mtTFA, NM_031326, forward primer: GAAAGCACAATACTCAAGAGG, reverse primer: CTGCTTTTCATCATGAGACAG) and the myocyte-enriched calcineurin interacting protein 1 (MCIP1, NM_004414, forward primer: GCCGCCATGTTATCCGTTGTG, reverse primer: GGTTGCCATCTTTCAGTTG). The glucose-6-phosphatase (housekeeping gene, GCB, NM_000157, forward primer: GCACAATT- TACGCTCCCAGA, reverse primer: CTTCCTATTACGGCTC- CATT) was used for normalization. Values of each gene were normalized to GCB mRNA content to compensate for variation in input RNA amounts and efficiency of reverse transcription and corrected for the amount of RNA relative to muscle weight (8).

Statistical analysis. Values are expressed as means ± SE. Determination of statistical significance of MI-PE treatment was accomplished by using a two-way ANOVA. When appropriate, differences between groups were tested with a Newman-Keuls post hoc test. Mortality rates were compared using the χ² test. Statistical significance was accepted at P < 0.05.

RESULTS

Survival. None of the sham-operated animals died during the study. None of the MI rats died by 1 mo postprocedure. MI rats...
showed significant mortality by 4 mo, with a mortality significantly higher in untreated group (5 of 13 rats died, 40%) compared with PE-treated group (2 of 10 rats died, 20%) \( (P < 0.05) \).

**Cardiovascular evaluations.** At the 7-day time point, all infarcted animals had similar myocardial infarction size demonstrated by a mean akinesia score of 4.2 ± 0.2 vs. 0 ± 0 in sham (Table 1).

At 1 mo, rats in the MI group had a 42% increase in LVEDD, suggesting significant LV remodeling \( (P < 0.05) \) and a high score of akinesia \( (\sim 50\% \text{ of the left ventricle}) \). This alteration was associated with a marked reduction of the cardiac contractility evaluated by the shortening fraction (FS, −59%; \( P < 0.05 \)) whereas blood pressure was not significantly modified.

Fig. 1. Maximal ADP-stimulated rates of respiration of mitochondria \( (V_{\text{max}}) \) in situ in permeabilized superficial gastrocnemius skeletal muscle, after 1 (A) and 4 (B) mo of treatment. Mitochondrial substrates were glutamate and malate \( (G + M) \), palmitoyl carnitine and malate \( (PC + M) \), glycerol-3-phosphate \( (G3P) \), or pyruvate and malate. Values are expressed as \( \mu \text{mol O}_2 \cdot \text{min}^{-1} \cdot \text{g fiber dry wt}^{-1} \). Values are means ± SE. Significantly different from sham: *\( P < 0.05 \); **\( P < 0.01 \); significantly different from MI: §§\( P < 0.01 \).

Importantly, PE significantly improved mitochondrial metabolic pathways as attested by the significant increase of the muscle \( V_{\text{max}} \) in the MI treated with PE compared with the nontreated MI rats \( (+57 \text{ and } +47\% \text{, respectively with glutamate-malate and pyruvate as substrates; } P < 0.001) \). Moreover, as \( V_{\text{max}} \) in MI-PE rats did not differ from Sham whatever the substrate used, this shows that PE treatment was able to normalize skeletal muscle mitochondrial function (Fig. 1B).

### Table 1. Hemodynamic parameters

<table>
<thead>
<tr>
<th>Treatment Duration</th>
<th>1 mo</th>
<th>4 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sham</td>
<td>MI</td>
</tr>
<tr>
<td>SAP, mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 9</td>
<td>n = 9</td>
<td>n = 9</td>
</tr>
<tr>
<td>128 ± 3</td>
<td>111 ± 6</td>
<td>119 ± 8</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>327 ± 7</td>
<td>356 ± 13</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>7.1 ± 0.1</td>
<td>10.1 ± 0.1†</td>
</tr>
<tr>
<td>LVESD, mm</td>
<td>4.4 ± 0.2</td>
<td>8.5 ± 0.3‡</td>
</tr>
<tr>
<td>FS, %</td>
<td>37 ± 2</td>
<td>15 ± 2</td>
</tr>
<tr>
<td>Score</td>
<td>0 ± 0</td>
<td>4.3 ± 0.3‡</td>
</tr>
</tbody>
</table>

Values are means ± SE. MI, myocardial infarction without treatment; MI-PE, myocardial infarction treated with perindopril; SAP, systolic arterial pressure; HR, heart rate; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; FS, fractional shortening; score, evaluation of the area of left ventricular akinesia. *\( P < 0.05 \) and †\( P < 0.01 \) vs. Sham; ‡\( P < 0.05 \) and §§\( P < 0.01 \) vs. MI.
The ACR was not different between MI (5.2 ± 0.7) and MI-PE rats (4.4 ± 0.1).

Similarly, muscle activities of citrate synthase, a Krebs cycle enzyme, and of cytochrome oxidase, complex IV of the respiratory chain, were significantly depressed at 4 mo in MI rats (9.3 ± 0.5 IU/g wet wt, $P < 0.05$, and 2.11 ± 0.06 IU/g wet wt, $P < 0.001$, respectively) compared with sham (11.9 ± 0.7 and 3.3 ± 0.1 IU/g wet wt, respectively) and fully recovered after PE treatment (10.9 ± 2.0 and 3.1 ± 0.6 IU/g wet wt, respectively, not significant vs. sham group).

mRNA levels of nuclear factors associated with mitochondrial biogenesis in Gas muscle. To evaluate whether alterations in Gas muscle mitochondrial function could be the consequence of alterations in mitochondrial gene expression, we assessed the mRNA levels of mitochondrial transcription factors 4 mo after MI. MI led to significant reductions in muscle mRNAs coding for the coactivator of transcription PGC-1α and for the transcription factor NRF-2α ($-54$ and $-45\%$, respectively, $P < 0.05$) and tended to reduce mtTFA ($-22\%$, $P = 0.06$) 4 mo after surgery (Fig. 2). Thus metabolic defects of skeletal muscle were associated with a decrease in the expression of key transcription factors involved in the regulation of mitochondrial biogenesis.

PE treatment significantly increased the mRNA levels of PGC1-α (+129% compared with MI, $P < 0.05$) and NRF-2α (+91% compared with MI, $P < 0.05$), whereas mtTFA showed a tendency to be increased (+50% compared with MI, $P < 0.06$). Then treatment with the ACEi restored the mRNA expression of all these factors, reaching the values of the Sham-operated animals.

Significant positive correlations ($P < 0.001$) were found between PGC-1α mRNA expression and both transcriptional factors mtTFA and NRF-2α ($r = 0.88$ and $r = 0.70$, respectively). Moreover, positive correlations ($P < 0.05$) were observed between PGC-1α mRNA content on one hand and muscle oxidative capacity ($V_{\text{max}}$, $r = 0.48$), mitochondrial marker cytochrome-c oxidase ($r = 0.65$), or citrate synthase activities ($r = 0.45$), on the other (Fig. 3).

Interestingly, the content of MCIP1 mRNA, which is a marker of calcineurin activation, was downregulated in the Gas after MI. It significantly recovered under ACEi (Fig. 4A).

**DISCUSSION**

The present investigation demonstrates that ACEi totally prevented the impairments of skeletal muscle mitochondrial function observed 4 mo after MI. Furthermore, the downregulation of gene expression of the mitochondrial transcriptional factors PGC-1α, NRF-2α, and mtTFA was also prevented, suggesting that ACEi protects skeletal muscle through a preservation of mitochondrial biogenesis.

**Cardiovascular and muscular effects of myocardial infarction.** MI-induced LV dysfunction was characterized by a significant LV dilatation and a reduced FS related to LV akinesia. Systemic blood pressure decreased significantly at 4 mo after MI, secondary to cardiac failure. Similar to other studies (2, 3, 14, 26), mitochondrial capacity, enzyme activities, and mitochondrial function were decreased in skeletal muscle of MI rats.

This study extends our knowledge of skeletal muscle energetics in heart failure by demonstrating that the three main
mitochondrial oxidation pathways (pyruvate, G3P, and glutamate-malate substrates) were functionally impaired. Accordingly, two markers of mitochondrial mass, citrate synthase and cytochrome oxidase, were also decreased. Recently, Ponsot et al. (19) have found that Gas poorly oxidizes palmitoyl carnitine. Our data indicate that oxidation rates of palmitoyl carnitine were not significantly modified after MI (see Fig. 1).

Interestingly, as in pressure overload-induced heart failure (8), MI-induced mitochondrial defects were associated with a decreased expression of transcription factors involved in the regulation of mitochondrial biogenesis. Thus expression of NRF-2α, for which recognition sites have been described on genes encoding mtTFA and mitochondrial proteins in rodents (21), and PGC-1α, which is the major positive factor of muscle mitochondrial biogenesis (8, 9, 29) functioning through its interaction with NRFs, were reduced in MI rats. The relationships observed between transcriptional factors implicated in the mitochondrial biogenesis and the muscle oxidative capacities suggest that the decreased oxidative capacity in skeletal muscle of MI rats results from diminished mitochondrial gene expression, linked to PGC-1α, NRFs, and mtTFA downregulation.

Cardiovascular and muscular effects of ACE inhibition. ACEi decreased mortality and significantly improved MI-induced cardiac dysfunction by limiting LV dilatation and LV wall akinesia, both 1 and 4 mo after surgery, supporting a beneficial effect of PE on infarction-induced cardiac failure. This is the first report that indicates that 4 mo of PE completely prevented the decreased ability of Gas mitochondria to oxidize metabolic substrates in MI rats. The efficacy of ACEI treatment was significant in all animals but exhibited a large range of effects from +20% to +85%. Skeletal muscle mitochondrial density is decreased in CHF (23, 26). Therefore, it is tempting to speculate that ACEi protected mitochondrial function through mitochondrial biogenesis. Indeed, mRNA levels of the main nuclear factors regulating mitochondrial biogenesis were preserved in treated MI rats. Moreover, positive correlations between the main factor controlling mitochondrial biogenesis, PGC-1α, and the skeletal muscle oxidative capacities were observed. A role for muscle deconditioning, which is known to affect PGC-1α expression and oxidative capacity, can be discarded for several reasons. First, Simonini et al. (23) showed that heart failure produces changes in skeletal muscle gene expression that cannot be explained by a decrease in activity. Second, and in accordance with another study (25), correlations between activity and the subsequently measured LV end-diastolic pressure, infarct size, and right ventricular weight were all poor (r > 0.16 for each relationship), indicating that the level of activity was not related to the severity of heart failure (23). Finally, ACEi treatment does not affect endurance capacity in normal rats (1). Thus we can certainly rule out that ACEi has a direct impact on the activity level of rats maintained in their cages. Taken together, our results suggest that the preserved expression of transcriptional factors implicated in mitochondrial biogenesis participate in the protecting effect of ACEi on skeletal muscle oxidative capacities.

Several hypotheses deserve to be discussed concerning the mechanisms involved in these results. It is unlikely that ACEi...
directly affected the expression of PGC-1α because ACEi did not improve maximal oxidative capacity of skeletal muscles, nor endurance time in normal rats (1). Similarly, a direct negative effect of angiotensin II on the transcriptional regulation of muscular metabolism could probably be ruled out. Indeed, ACEi failed to protect skeletal muscle energetic metabolism in a model of chronic LV dysfunction induced by aortic stenosis, likely due to chronic inadequate peripheral microcirculation downstream from the clip (16). In this regard, some tissue effects of ACE inhibitors (i.e., restoration of endothelial function, decrease in oxidative stress, and increase in muscular capillary density) have been demonstrated in both experimental models and human studies (7) and could be linked to the metabolic protective effects of ACEi, because all potentially could activate intracellular cascades participating in oxidative metabolism regulation.

Relative to the signaling pathways, modulation of gene expression by the calcium-sensitive phosphatase calcineurin is largely involved in the remodeling of skeletal muscle. Recent data suggest that PGC-1α is a target of calcineurin (13), contributing to muscle fiber-type determination and formation of slow-twitch muscle fibers (10). MCIP1 is a marker of calcineurin activation in vivo because its expression is rapidly and robustly regulated by calcineurin (31). In the present investigation, skeletal muscle expression of MCIP1 was determined in all rodents. Interestingly, MCIP1 was decreased after MI, and ACEi treatment was able to weaken this decrease. Our data suggest that, first, calcineurin activity is decreased in skeletal muscle after MI, and second, ACEi preserves calcineurin activation. This result compares well with preserved MCIP1 expression in CHF patients under ACEi therapy, having normal oxidative capacity and expression of mitochondrial transcription factors (9). However, it is not possible at present to establish a cause-and-effect relationship between calcineurin activation and PGC-1 expression. Although our data suggest that calcineurin activation may participate in the changes in skeletal muscle mitochondrial function in heart failure and in the beneficial effects of ACEi, further studies using gain and loss of function of calcineurin would be necessary to make stronger statements.

Clinical relevance of these results. Although it was widely accepted that heart failure patients exhibit decreased skeletal muscle mitochondrial activity (6, 14, 24, 27), recent studies on ACEi-treated CHF patients failed to observe alterations in mitochondrial function, mitochondrial enzyme activity, or expression of mitochondrial proteins or transcription factors in skeletal muscles, compared with sedentary controls (15, 28). The present results may shed light on these apparently contradictory observations, by showing that ACEi treatment, missing in the previous studies, is able to reduce skeletal muscle metabolic derangements by preventing the decrease in gene expression of mitochondrial proteins. Thus ACEi treatment given early after infarction prevents the development of the myopathy. Whether ACEi could reverse the skeletal muscle metabolic myopathy, if given later after infarction, remains to be studied. Moreover, AT1 receptor antagonists use might be interesting to further investigate the mechanisms protecting the skeletal muscle mitochondrial function.

In conclusion, this study shows that chronic treatment with ACEi after myocardial infarction protects the mitochondrial function of skeletal muscle through a preservation of mitochondrial protein expression. Our data underscore the importance of ACEi therapy in heart failure patients and improve the knowledge concerning the protection of skeletal muscle metabolism. This could help to adapt strategies aiming to ameliorate the rehabilitation of the numerous patients suffering from chronic diseases associated with exercise intolerance and impaired skeletal muscles functions. Future studies will therefore be useful to further define the precise mechanisms mediating such ACEi-induced beneficial effect on skeletal muscle energetics.

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