Bioenergetic Protection of the Failing Atrial and Ventricular Myocardium by the Vasopeptidase Inhibitor Omapatrilat

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Abstract

Deficient bioenergetic signaling contributes to myocardial dysfunction and electrical instability in both atrial and ventricular cardiac chambers. Yet, approaches capable to prevent metabolic distress are only partially established. Here, in a canine model of tachycardia-induced congestive heart failure, we compared atrial and ventricular bioenergetics and tested the efficacy of metabolic rescue with the vasopeptidase inhibitor omapatrilat. Despite intrinsic differences in energy metabolism, failing atria and ventricles demonstrated profound bioenergetic deficiency with reduced ATP and creatine phosphate levels, and compromised adenylate kinase and creatine kinase catalysis. Depressed phosphotransfer enzyme activities correlated with reduced tissue ATP levels, while creatine phosphate inversely related with atrial and ventricular load. Chronic treatment with omapatrilat maintained myocardial ATP, the high-energy currency, and protected adenylate and creatine kinase phosphotransfer capacity. Omapatrilat-induced bioenergetic protection was associated with maintained atrial and ventricular structural integrity, albeit without full recovery of the creatine phosphate pool. Thus, therapy with omapatrilat demonstrates benefit in protecting phosphotransfer enzyme activities and preventing impairment of atrial and ventricular bioenergetics in heart failure.

Key words: atria, ventricle, adenylate kinase, creatine kinase, energy metabolism, heart failure
Introduction

Adequate myocardial bioenergetic infrastructure and optimal metabolic signaling are essential in supporting atrial and ventricular performance (12, 17, 20, 22, 53). In pathological conditions of hemodynamic load imposed on cardiac chambers, activation of the renin-angiotensin-aldosterone system (RAAS) leads to a cascade of cellular events, including oxidative distress, that are deleterious to metabolic wellbeing (48). Progression of distress is accelerated by a relative deficiency of the natriuretic peptide system that normally counteracts RAAS involvement (6). To circumvent humoral alterations that precipitate the syndrome of heart failure, a class of therapeutics has been developed that inhibits excessive activation of the RAAS system while potentiating the natriuretic peptide system. Collectively referred as vasopeptidase inhibitors (VPI), these agents - exemplified by the prototype omapatrilat - simultaneously inhibit the angiotensin-converting enzyme, critical in promoting the RAAS pathway, and the neutral endopeptidase, required for natriurtetic peptide degradation (4, 7, 52). Omapatrilat has shown initial promise in patients with heart failure, with favorable outcome on cardiac function (4). However, clinical trials have not produced definitive results (57), urging further investigation of the cardioprotective efficacy of omapatrilat use (54). In particular, little is known on the metabolic effects of omapatrilat, in either atria or ventricles, which would be of value in the setting of neurohumoral dysregulation associated with heart failure (27, 28, 54).

Previous studies indicate differences in energy metabolism in cardiac chambers (1, 3, 26, 39, 40), and show linkage between bioenergetic deficit and decompensation of heart performance (11, 12, 15, 29, 33, 43, 44, 53, 56) with potential benefit afforded by angiotensin-converting enzyme inhibitors (29). The bioenergetic profile of the failing atrium versus ventricle, especially in large animal models that closely mimic human heart failure, has however not been fully established, and it remains unknown whether strategies that inhibit RAAS would prevent metabolic distress imposed with disease (2,
Thus, the objective of the present study was to characterize the bioenergetic response to pressure and volume overload of atria and ventricles in experimental congestive heart failure, and establish the effectiveness of pharmacotherapy in preserving cardiac energetic parameters, including phosphotransfer enzyme function, using the prototypic vasopeptidase inhibitor omapatrilat.

**Methods**

Procedures were designed in accordance with the National Institutes of Health guidelines, and approved by the Mayo Institutional Animal Care and Use Committee.

**Experimental heart failure.** Congestive heart failure was produced in 18 male dogs by progressive rapid right ventricular pacing (46, 47, 55). Eight out of 18 dogs received omapatrilat therapy (CHF+OMA group). The remaining 10 dogs received no pharmacotherapy (CHF group). Dogs were anesthetized with sodium pentothal (20 mg/kg) and isoflurane (0.5-2.5%), and ventilated. An epicardial pacing lead was placed on the right ventricle via thoracotomy and connected to a generator (Medtronic Legacy 8161/8165). After a two-week long recovery, incremental ventricular pacing was imposed at 180 beats per min for 14 days followed by pacing at 200, 220 and then 240 beats per min for one week each for a total of five weeks of pacing. In the treated group, omapatrilat (10 mg/kg, twice a day orally) was initiated at the start of the pacing protocol. Six normal dogs served as controls.

**Echocardiography.** Cardiac ultrasound was performed in sinus rhythm in the conscious standing state. Left ventricular dimension (LVD) and ejection fraction (LVEF) were measured by two-dimensional guided M-mode (47, 55). The LVD index, left atrial area index and the mitral regurgitant jet size were measured from two-dimensional images in the parasternal long and short axis views. Images were digitally acquired and analyzed off-line (GE system 5 Horten, Norway). Five averaged measurements are reported for each parameter.
**Hemodynamics.** To record hemodynamic parameters the pacemaker was turned-off. Dogs anesthetized with pentobarbital (25 mg/kg in the control group and 12.5 mg/kg in the heart failure groups supplemented with 50 mg bolus titrated to effect) were intubated and ventilated. A Swan-Ganz catheter was advanced to the pulmonary artery *via* the right external jugular vein. Pressures and cardiac output readings were repeated at least three times and averaged. A high-fidelity Millar catheter was advanced to the left ventricle *via* the right femoral artery. Left ventricular pressure recordings were stored digitally and analyzed off-line (Sonoview, London, Canada). The femoral artery pressure was measured and monitored throughout.

**Bioenergetic profiling.** Following sternotomy, the pericardium was opened and atrial biopsies were obtained from the right and left atrial appendages and free walls, while ventricular biopsy was from the anterior left ventricular wall. For atrial biopsies, tissue to be harvested was surrounded with sutures, and samples snipped with sutures tightened to achieve hemostasis. For ventricular biopsy, an electrical biopsy drill (4 mm in diameter) was used to penetrate the anterior wall and secure the whole thickness of ventricular tissue (8). Tissue samples were immediately frozen in liquid nitrogen, pulverized in liquid nitrogen and extracted in a solution containing 0.6 M HClO₄ and 1 mM EDTA as described (15). Proteins were pelleted by centrifugation and protein content determined with a DC protein assay kit (Bio-Rad). Extracts were neutralized with 2 M KHCO₃. Creatine phosphate levels were measured using coupled enzyme assays with fluorometric detection (11). Myocardial ATP, ADP, GTP and GDP concentrations were determined by high-performance liquid chromatography (8, 15). Inorganic phosphate (Pᵢ) levels were measured using the EnzChek Phosphate Assay kit (Molecular Probes). The activities of creatine kinase and adenylate kinase were measured by spectrophotometry (11, 34). Total tissue creatine was measured using a colorimetric procedure after mild acid hydrolysis of creatine phosphate (10). The free creatine value was obtained by subtracting creatine phosphate from total creatine
content. Electrophoretic separation and quantitation of creatine kinase isoforms in myocardial extracts, stored in liquid nitrogen, was done using the Hydragel ISO-CK K20 kit (Sebia, Inc).

**Statistical analysis.** Comparisons between groups were completed with the ANOVA variance analysis or alternatively with the Wilcoxon rank-sum test. The significance of correlation between parameters was examined using the Pearson correlation coefficient if data were normally distributed or the Spearman's correlation coefficient if not. A P-value <0.05 was predetermined.

**Results**

**Atrial versus ventricular bioenergetic profiles.** Catalytic activities of the major phosphotransfer enzymes, creatine kinase and adenylate kinase, were consistently higher in the normal left ventricle compared to the normal atrium, i.e., by 2.8- and 1.6-fold respectively (n=6; p<0.001, Table 1). The normal ventricular myocardium had also a higher creatine kinase over adenylate kinase activity ratio compared to normal atria, i.e., 32 versus 19, respectively, indicating a larger contribution of creatine kinase-catalyzed phosphotransfer supporting ventricular energy metabolism. Ventricular compared to atrial myocardium displayed a higher mitochondrial creatine kinase CKmit isoform fraction, 13±1% versus 5±1%, respectively (p<0.01). Conversely, atrial myocardium compared to ventricular tissue contained higher creatine kinase CK-BB and CK-MB isoform fractions, 3±1% and 16±1% versus 1±1 and 8±1%, respectively (p<0.01). Myocardial ATP, GTP, creatine phosphate (CrP) and total creatine (Cr) levels were higher in left ventricular biopsies than in corresponding atrial samples, by 1.9, 1.4, 1.9 and 1.8-folds respectively (p=0.003, 0.001, 0.003 and 0.001; Table 1). In addition, ATP/ADP, GTP/GDP and CrP/Pi ratios were all higher in the left ventricle compared to atrial tissue, indicating overall a higher ventricular energetic potential. Taken together, higher creatine kinase and adenylate kinase activities and elevated ATP/ADP and
CrP/P\textsubscript{i} ratios in the ventricular myocardium may indicate efficient metabolic cycling between ATP-generating and ATP-consuming sites compared to atrial muscle. Thus, direct comparison of atria \textit{versus} ventricles indicates unique energetic profiles of cardiac chambers, with ventricles characterized by an apparently more robust energetic potential and phosphotransfer ability to control ATP/ADP ratios in subcellular locales.

**Altered bioenergetics in failing myocardium.** Chronic pacing induced significant left ventricular systolic dysfunction, left ventricular dilatation and hypertrophy, as well as left atrial dilatation, typical signs of heart failure (Table 2). As a consequence, left ventricular end-diastolic filling pressure and pulmonary capillary wedge pressure were significantly increased in the CHF group (Table 2). Mild to moderate mitral regurgitation was also uniformly observed, characteristic of overt heart failure. Atrial and ventricular biopsies from failing hearts displayed profound bioenergetic deficiencies, characterized by a reduced phosphotransfer capacity coupled with a significant nucleotide imbalance (Figure 1 and Figure 2). The main energy reserve molecule, creatine phosphate, was markedly decreased, by 70%, in failing atrial and ventricular specimens (p<0.05, Figure 1 and Figure 2). This reduction was accompanied by depletion of total creatine content, by 48% and 55%, in atria and ventricles respectively (p<0.05). The creatine phosphate/creatine ratio, which in control atria and ventricle was 1.1±0.1 and 1.3±0.1, in heart failure was reduced to 0.6±0.1 and 0.5±0.1 (p<0.01), respectively (Table 1). The principal energetic currency ATP was also reduced by 35% (p<0.05) in failing atria, and by 23% (p<0.05) in failing ventricles. Myocardial GTP levels remained unchanged indicating a preserved biosynthetic capacity in atria and ventricles. Ventricular adenylate kinase and creatine kinase activities, however, were diminished by 38% (p<0.05) and 42% (p<0.01), respectively compared to normal hearts. Atrial adenylate kinase and creatine kinase activities in failing hearts were lower by 21% (p<0.05) and 23% (p=0.09), respectively compared to normal hearts. In heart failure, in atrial and ventricular myocardium the CKmit isoform fraction dropped to 3±1% and
9±1% of total creatine kinase activity, a reduction of 41% and 34% (p<0.01), respectively, while the CK-MB fraction increased to 22±1% and 13±1%, respectively. Thus, heart failure is associated with a significant bioenergetic deficit and remodeling of creatine kinase isoform composition in both atrial and ventricular chambers.

**Omapatrilat prevents maladaptive remodeling, preserves high-energy substrates and phosphotransfer capacity in heart failure.** Chronic treatment with the vasopeptidase inhibitor omapatrilat significantly reduced atrial and ventricular remodeling, indicated by the attenuation of left ventricular and left atrial dilation as well as by the reduction of myocardial hypertrophy (Table 2). Hemodynamics, measured at the trough level of omapatrilat treatment 12 h after the last dose, were similar in the treated and untreated groups (Table 2). Compared to untreated failing hearts, chronic omapatrilat treatment protected myocardial levels of ATP, and the catalytic activities of adenylate kinase and creatine kinase in both atria and ventricles (Figure 1 and Figure 2). In omapatrilat-treated hearts, these bioenergetic parameters remained essentially at control levels despite the imposed load of heart failure, suggesting a significantly lower presence of damaging factors and/or an improved protection from protease activity or oxidant injury (5, 28, 37). In fact, high-energy ATP levels and the phosphotransfer catalytic activities of adenylate kinase and creatine kinase, which closely paralleled, were substantially reduced in heart failure but significantly improved by omapatrilat therapy (Figure 3A and Figure 3B). Despite omapatrilat treatment, however, reduction in creatine phosphate levels was still persistent although creatine kinase activity per se was fully maintained. This was associated with poor recovery of the CKmit isoform fraction, to 4.1±0.4% in atria and to 9.9±0.8% in ventricles, not significantly different from untreated failing hearts. The total myocardial creatine content was also only partially improved with omapatrilat treatment, and remained lower by 30% and 45% (p<0.05) in atria and ventricles, respectively, compared to values in corresponding heart chambers from controls (Table 1). A persistent deficit in creatine metabolism, after
omapatrilat treatment, may indicate a possibly dysfunctional creatine transporter (50) and/or creatine kinase-adenine nucleotide translocator functional interaction at the mitochondrial site, which would compromise creatine phosphate generation despite the recovery of total creatine kinase activity (25). Along with this suggestion are lower atrial and ventricular creatine phosphate/creatine ratios, which after omapatrilat treatment were $0.7\pm0.1$ and $0.6\pm0.1$, respectively ($p<0.05$). Since cellular ATP levels recovered to near control values, this suggests that the mitochondrial content and the ATP production capacity were maintained with omapatrilat treatment. Creatine phosphate levels were inversely proportional to pulmonary capillary wedge pressure (PCWP) and left ventricular end-diastolic pressure (LVEDP), indicating that this bioenergetic parameter reflects myocardial energy consumption and energy delivery through the creatine kinase-creatine phosphate shuttle depending on the degree of atrial or ventricular load (Figure 3C and 3D). Thus, although it may fall short in supporting in its entirety the whole bioenergetic system of a cardiomyocyte, chronic treatment with the vasoepitidase inhibitor omapatrilat prevents the impairment of several critical atrial and ventricular energetic parameters characteristic of the failing heart.

**Discussion**

This study shows that congestive heart failure produces significant bioenergetic deficits in atria and ventricles preventable, to a large extend, by chronic treatment with the vasoepitidase inhibitor omapatrilat. Although the normal ventricle exhibited a higher energetic potential, compared to the atrium characterized by a lower energetic potential and a lower phosphotransfer capability to control ATP/ADP ratios, both myocardial chambers responded to heart failure with a severe but overall similar maladaptive rearrangement in cell bioenergetics. Yet, ATP levels and phosphotransfer enzyme activities in both atria and ventricles were effectively protected by omapatrilat, indicating
that this prototypic vasopeptidase inhibitor is useful in maintaining metabolic homeostasis in heart failure.

This study compared side-by-side atrial and ventricular energetic metabolism in a large animal model. Myocardial ATP, creatine phosphate, total creatine and phosphotransfer enzymes in the normal ventricle were found two fold-higher compared to the normal atrium. Ventricular myocardium displayed a higher mitochondrial creatine kinase CKmit fraction compared to atrial tissue. Conversely, atrial myocardium contained higher CK-BB and CK-MB isoform fractions, in line with previous reports (1, 26). This is in accord with the notion that the vigorous contractility of the ventricle, compared to a rather more passive atrial chamber with a thinner wall, requires a higher rate of energy supply to fulfill a sustained pumping function. Moreover, tissue content of inorganic phosphate in the ventricle was less than half of that in the atrium, reflecting a requirement for a higher phosphorylation potential and energy of ATP hydrolysis (7, 29, 49) to support ventricular contractility.

The syndrome of heart failure, induced here by rapid ventricular pacing, is a generalized model of dilated cardiomyopathy in the intact animal, characterized by atrial and ventricular dilatation with severely depressed left ventricular systolic function and increased left ventricular filling pressure (8, 55). With the challenge of heart failure, profound bioenergetic deficits were manifested in the ventricle by the reduced activities of phosphotransfer enzymes, depletion of high-energy phosphoryls, and reduction in cellular energetic potential. This is in accord with reports that demonstrate ventricular energetic abnormalities as a metabolic denominator of cardiovascular disease (11, 12, 15, 18, 20, 21, 29, 30, 49). In cardiomyopathy, the increase in wall stress (dilatation) and muscle mass (hypertrophy) raises the myocardial energy demand while reducing the availability of myocardial energy supply due to increased intercapillary distance, fibrosis and myocyte diameter (22, 32). As reported in cardiomyopathic models, the energy reserve stored in the form of creatine phosphate, a key component of the high-
energy phosphoryl pool, is first depleted to preserve ATP which is directly utilized for myocardial contraction and electrical integrity (18, 30, 31). In fact, the present study indicates that creatine phosphate, rather than ATP levels per se or the activities of the phosphotransfer enzymes creatine kinase and adenylate kinase, inversely relate to myocardial wall stress of atrial and ventricular chambers, indicating that this metabolic marker reflects altered energy consumption and creatine kinase flux associated with myocardial load (17, 56). We here demonstrate the profile of bioenergetic distress in failing atria, with induced changes directionally comparable to those observed in ventricles in accord with previous reports (26). Depletion of ATP linearly corresponded to a marked reduction of creatine kinase and adenylate kinase activities in both failing atria and ventricles, indicating simultaneous and parallel impairment in total ATP content and in the capacity of high-energy phosphoryl transfer. This observation supports the notion that reduction of creatine kinase and adenylate kinase activities, two enzymes that facilitate ATP delivery and promote removal of ADP, inorganic phosphate and protons from cellular ATPases, engage the failing myocardium into a state of phosphotransfer deficit. The mechanisms responsible for ATP reduction in the failing myocardium may involve depletion of the adenine nucleotide pool in a compensatory role to sustain the phosphotransfer potential and the ATP-to-ADP ratio (43). Ultimately, however, the inability of the failing myocardium to sustain ATP and creatine phosphate levels leads to depletion of intracellular high-energy phosphoryls (11, 16, 20, 53), contributing to organ failure.

These findings reflect the dependence of cardiac performance not necessarily on concentrations of molecules carrying high-energy phosphoryls or on phosphotransfer enzyme activity but rather on the actual flux of high-energy phosphoryls (12, 20, 29, 30, 36, 53). Optimal function and communication between components of the bioenergetic cellular system is a requisite for performance supported by complementation in phosphotransfer enzyme activity and intimate interaction of phosphotransfer proteins.
with cellular sites of metabolic sensing and/or transduction (12, 15, 35, 42). In failing hearts a reduction in creatine kinase flux is associated with dysfunction in metabolic sensors despite a compensatory increase in adenylate kinase flux or glycolytic potential (15, 18, 45). Although a deficit in creatine kinase compromises energetic efficiency (16, 38), the plasticity in cellular bioenergetics maintains myocardial function, even at low ATP levels, providing that phosphotransfer systems are operational (19, 24). Here, we demonstrate that the total phosphotransfer capacity correlates with myocardial creatine phosphate and ATP levels. This indicates that a higher creatine kinase and adenylate kinase-mediated catalysis is necessary to maintain high-energy phosphoryl-carrying pools, apparently through re-phosphorylation, thus preventing loss by degradation and/or through efflux pathways (34-36, 50). This is in accord with phosphotranfer enzyme knockout studies where genetic ablation of a single isoform compromises the cellular adenine nucleotide content (34).

Significantly, we revealed a previously unrecognized aptitude of omapatrilat treatment to maintain ATP levels and the phosphoryl transfer function of creatine kinase and adenylate kinase in failing atria and ventricles. Such favorable outcome could, in principle, relate to the established omapatrilat-induced prevention of remodeling via vasopeptidase inhibition (7, 29), reducing oxidative stress and demands of myocardial mechanics for high-energy ATP. Organ failure gives rise to a vigorous neurohumoral response, exaggerated renin-angiotensin-aldosterone system (RAAS) activity, insufficiency of the natriuretic peptide system, and an excess in circulating levels of catecholamines (51). The class of vasopeptidase inhibitors, exemplified by omapatrilat, suppresses RAAS while accentuating plasma natriuretic peptides through combined inhibition of the angiotensin converting enzyme and vasopeptidase activity (4, 5, 51). Chronic intervention with omapatrilat reduced atrial and ventricular chamber dilatation and decreased myocardial mass, indicating a significant pressure and volume unloading effect in the setting of congestive heart failure. Moreover, omapatrilat also preserved
transcellular high-energy transfer by maintaining adenylate kinase and/or creatine kinase activity to compensate for the ATP requirements of the failing myocardium at the expenses of energy reserve. Such metabolic benefit is further supported by the observation of improved myocardial ATP content in omapatrilat-treated versus untreated failing hearts. These findings are in line with reports that suggest an ability of angiotensin-converting enzyme inhibitors to attenuate oxidant damage and preserve heart mitochondrial function (9, 37). It has also been recognized that CKmit is among the most sensitive enzymes to oxidative damage (41), and was not fully protected by omapatrilat treatment. Poor protection of CKmit activity and of total creatine content could explain the uncompensated deficit in the creatine phosphate pool with therapy in heart failure. Despite the absence of full protection of the whole energetic system, the present findings reveal a distinct metabolic advantage of omapatrilat-therapy, and provide evidence for potential benefits that are beyond an exclusive action of the drug on neurohumoral regulation (27, 28, 54).

In summary, the present study demonstrates differences in the bioenergetic profiles of atrial versus ventricular myocardium in a large animal model, and marked metabolic derangements in both chambers in the syndrome of heart failure. Omapatrilat, a multipotent vasopeptidase inhibitor, is here identified to possess bioenergetic anti-remodeling effects, preserving myocardial phosphotransfer enzyme activities and ATP levels while maintaining atrial and ventricular structural integrity under the stress of heart failure. This previously unrecognized benefit of omapatrilat on energy metabolism identifies a potentially useful therapeutic approach in preserving the myocardial energetic balance in the setting of heart failure.
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References


Figure legends

**Figure 1** Omapatrilat treatment prevents heart failure (CHF)-induced reduction in atrial myocardial creatine kinase (A) and adenylate kinase (B) activities and ATP levels (C), with limited effect on creatine phosphate (CrP) levels (D). * P<0.05 vs control, # P<0.05 versus CHF.

**Figure 2** Omapatrilat treatment prevents CHF-induced decline in left ventricular (LV) myocardial creatine kinase (A) and adenylate kinase (B) activities and ATP levels (C), yet does not restore creatine phosphate levels (D). * P<0.05 vs control, # P<0.05 versus CHF.

**Figure 3** Linkage among bioenergetic parameters, and between bioenergetics and myocardial performance in atria and ventricle. A and B - correlation between left ventricular (LV) ATP concentration and creatine kinase (CK) and adenylate kinase (AK) activities (B). C and D - correlation between pulmonary capillary wedge pressure (PCWP) and atrial creatine phosphate (CrP), and between LV end-diastolic pressure (LVEDP) and LV CrP in control, CHF and treated (omapatrilat) CHF dogs. *P<0.05, ** P<0.01
### Table 1: Atrial and left ventricular bioenergetic profiles in controls

<table>
<thead>
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<th>Parameters</th>
<th>Atria n=6</th>
<th>LV n=6</th>
<th>LV/A ratio</th>
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<tr>
<td>Creatine kinase</td>
<td>5.25±0.52</td>
<td>13.6±1.37**</td>
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<tr>
<td>Adenylate kinase</td>
<td>0.28±0.02</td>
<td>0.43±0.02**</td>
<td>1.6</td>
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<td>CK/AK ratio</td>
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<td>ATP</td>
<td>17.3±0.7</td>
<td>30.3±2.95**</td>
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<td>ATP/ADP</td>
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<td>6.06*</td>
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<tr>
<td>GTP</td>
<td>0.86±0.05</td>
<td>1.18±0.09*</td>
<td>1.4</td>
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<tr>
<td>GTP/GDP</td>
<td>4.09</td>
<td>6.94*</td>
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<td>Creatine phosphate</td>
<td>31.3±2.5</td>
<td>57.7±6.8**</td>
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<td>Total creatine</td>
<td>58.7±4.1</td>
<td>103±7.2**</td>
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<tr>
<td>CrP/Cr</td>
<td>1.14</td>
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<td>CrP/P&lt;sub&gt;i&lt;/sub&gt;</td>
<td>1.08</td>
<td>5.06**</td>
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Values are means±SE from total atrial and left ventricular (LV) muscle. Enzyme activities are expressed in μmol·min<sup>-1</sup>mg protein<sup>-1</sup>, metabolite levels in nmol·mg protein<sup>-1</sup>. *P<0.05 vs atria; **P<0.01 versus atria.
**Table 2:** Effects of omapatrilat on hemodynamic and structural remodeling in heart failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n=6)</th>
<th>CHF (n=6)</th>
<th>CHF+OMA (n=8)</th>
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<td>PCWP, mm Hg</td>
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<td>20.4±1.5†</td>
<td>14.3±2.2†</td>
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<td>LVSP, mm Hg</td>
<td>153±7</td>
<td>119±7†</td>
<td>110.0±4†</td>
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<td>LVEDP, mm Hg</td>
<td>4.9±2.0</td>
<td>28.1±5.1†</td>
<td>22.1±2.0†</td>
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<tr>
<td>+dP/dt</td>
<td>2,783±275</td>
<td>1,675±191†</td>
<td>1,332±53†</td>
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<tr>
<td>Tau</td>
<td>28.1±3.3</td>
<td>72.4±20.8†</td>
<td>78.0±6.9†</td>
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<tr>
<td>LVEF</td>
<td>0.66±0.03</td>
<td>0.31±0.04†</td>
<td>0.29±0.02†</td>
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<td>LA area index, mm²/kg</td>
<td>0.60±0.04</td>
<td>0.91±0.06†</td>
<td>0.71±0.04‡</td>
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<td>LV dimension index, mm/kg</td>
<td>0.18±0.01</td>
<td>0.21±0.01†</td>
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<tr>
<td>LV mass index, g/kg</td>
<td>4.2±0.2</td>
<td>5.0±0.2†</td>
<td>4.3±0.1‡</td>
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</table>

CHF, congestive heart failure; dP/dt, peak rate of left ventricular pressure change; LA, left atrial; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; LVSP, left ventricular systolic pressure; OMA, omapatrilat; PCWP, pulmonary capillary wedge pressure; Tau, time constant of LV relaxation. Values are mean±SE; †P<0.05 versus control; ‡P<0.05 CHF+OMA versus CHF.
Atrial bioenergetics

Figure 1
LV bioenergetics

Figure 2
ATP and CK

\[ r^2 = 0.52^{**} \]

ATP and AK

\[ r^2 = 0.56^{**} \]

PCWP and CrP level

\[ r^2 = 0.38^{**} \]

LVEDP and CrP level

\[ r^2 = 0.50^{**} \]

Figure 3