Angiotensin II–Converting Enzyme Inhibition Improves Survival, Ventricular Remodeling, and Myocardial Energetics in Experimental Aortic Regurgitation

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Background—Aortic valve regurgitation (AR) is a volume-overload disease causing severe eccentric left ventricular (LV) hypertrophy and eventually heart failure. There is currently no approved drug to treat patients with AR. Many vasodilators including angiotensin-converting enzyme inhibitors have been evaluated in clinical trials, but although some results were promising, others were inconclusive. Overall, no drug has yet been able to improve clinical outcome in AR and the controversy remains. We have previously shown in an animal model that captopril (Cpt) reduced LV hypertrophy and protected LV systolic function, but we had not evaluated the clinical outcome. This protocol was designed to evaluate the effects of a long-term Cpt treatment on survival in the same animal model of severe aortic valve regurgitation.

Methods and Results—Forty Wistar rats with AR were treated or untreated with Cpt (1 g/L in drinking water) for a period of 7 months to evaluate survival, myocardial remodeling, and function by echocardiography as well as myocardial metabolism by µ positron emission tomography scan. Survival was significantly improved in Cpt-treated animals with a survival benefit visible as soon as after 4 months of treatment. Cpt reduced LV dilatation and LV hypertrophy. It also significantly improved the myocardial metabolic profile by restoring the level of fatty acids metabolic enzymes and use.

Conclusions—In a controlled animal model of pure severe aortic valve regurgitation, Cpt treatment reduced LV remodeling and LV hypertrophy and improved myocardial metabolic profile and survival. These results support the need to reevaluate the role of angiotensin-converting enzyme inhibitors in humans with AR in a large, carefully designed prospective clinical trial. (Circ Heart Fail. 2013;6:1021-1028.)

Key Words: aortic valve insufficiency ■ captopril ■ heart ventricles ■ hypertrophy ■ metabolism ■ volume overload

Aortic valve regurgitation remains a disease without any proven effective treatment.1 Patients with severe aortic valve regurgitation (AR) will develop over time severe left ventricular (LV) dilatation, eccentric hypertrophy, and eventually heart failure (HF). The current treatment strategy is essentially to wait-and-see, with a careful serial clinical and echocardiographic follow-up to detect progressive LV dilatation, decrease of LV function, or occurrence of symptoms that would mandate aortic valve replacement surgery.1 Many clinical trials have evaluated the efficacy of various drugs with vasodilator properties in the treatment of severe AR.2,3 Unfortunately, their results have been inconclusive. Angiotensin-converting enzyme inhibitors (ACEI) were tested in AR, but conflicting results were obtained. It has been suggested that trial design and/or patient selection may be at least, in part, responsible for the inconsistency of the results.4 We have previously shown in a controlled animal model of pure severe aortic valve regurgitation that ACEI captopril (Cpt) reduced LV hypertrophy and protected LV systolic function.5,6 However, we could not provide a clear mechanism to explain those protective effects. We also had not evaluated the effects of the treatment on the long-term clinical outcome of the animals treated with Cpt. This study was, therefore, designed to evaluate whether Cpt treatment improved survival in rats with severe aortic valve regurgitation. We also evaluated the effects of Cpt on LV remodeling, hypertrophy as well as on myocardial metabolism in search of a potential protective mechanism.

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Methods

Animals

Sixty adult Wistar rats were purchased from Charles River and divided into 3 groups: normal sham-operated (sham; n=18), untreated with aortic regurgitation (AR; n=25), and Cpt-treated with AR (n=21; 1 g/L in drinking water). Treatment with Cpt was initiated...
2 weeks after the AR induction. All animals were evaluated daily by experienced technicians for the detection of signs of respiratory distress or pain. Animals were weighed weekly. Animals with respiratory distress were quickly euthanized. The protocol was approved by the Université Laval's Animal Protection Committee and followed the recommendations of the Canadian Council on Laboratory Animal Care.

Aortic Regurgitation
Severe AR induced by retrograde puncture of the aortic valve leaflets under 1.5% inhaled isoflurane anesthesia as previously described.7,8 Sham animals had their right carotid artery cannulated under anesthesia without puncture of the aortic valve. Animals were clinically evaluated daily by experienced animal laboratory technicians for the presence of signs of HF (increased respiratory rate/distress and/or peripheral edema) and were weighed weekly. At the end of the protocol surviving animals were euthanized, hearts were quickly dissected, and all cardiac chambers were weighed. LVs were snap-frozen in liquid nitrogen and kept at −80°C for further analysis.

Echocardiography
A complete M-Mode, 2D, and Doppler echocardiogram was performed on the animals under 1.5% inhaled isoflurane anesthesia using a 12-MHz probe with a HDI11XE echograph (Philips Medical Imaging, Andover, MA) immediately before and during surgery, after 3 and 6 months. The echocardiographic after 2 weeks was performed to quantify AR before starting the protocol to ensure all animals still met the entry criteria. LV dimensions, wall thickness, fractional shortening, diastolic function, cardiac output, and myocardial performance index were evaluated as previously reported.5-10

Small Animal PET Protocol
Imaging experiments and data analysis were performed essentially as described before.11-14 Images were acquired using either a LabPET avalanche photodiode–based small animal positron emission tomography (PET) scanner having a 4-cm axial field of view (FOV) or a Triumph dual modality PET/computed tomography scanner having a 28-cm axial FOV (Gamma Medica, Northridge, CA) at the Sherbrooke Molecular Imaging Center. Care was taken to consistently use the same scanner for a given animal. Briefly, under isoflurane anesthesia (1-1.5% at 1 L/min oxygen flow), a catheter was installed in the caudal vein for the administration of the radiotracer. The animal was then positioned with the heart in the center of the scanner FOV and a 45-minute–gated dynamic acquisition was started 60 seconds before [18F]-fluorothioheptadecanoic acid ([18F]-FTHA; 30–40 MBq, in 0.3 mL+0.1 mL flush of 0.9% NaCl, respectively) was injected via the caudal vein over 30 seconds. The animal was returned in his cage after each scan. Image dynamic data analysis was performed as described previously.15 Myocardial nonesterified fatty acid uptake and myocardial nonesterified fatty acid fractional uptake were determined by a Patlak graphical analysis of the [18F]-FTHA data.

LV Volumes and Ejection Fraction
The analysis was performed by dividing the cardiac cycle into 8 gates on the basis of the R-R intervals using the last 15 minutes of the [18F]-FTHA list-mode dynamic–gated acquisition. The analysis yielded the left end-systolic (ESV) and end-diastolic (EDV) volumes from which the stroke volume (SV) and ejection fraction (EF) were computed as SV=EDV−ESV and EF=100×SV/EDV, respectively. The Corridor4DM software from Segami Oasis (Columbia, MD) was used for reorientation and cardiac data analysis, as previously described.14

Enzymatic Activity Determinations
LV samples were kept at −80°C until assayed for maximal (V_{max}) enzyme activities. Small pieces of LV (20–30 mg) were homogenized in a glass–glass homogenizer with 9 or 39 volumes of ice-cold extraction medium pH 7.4 (250 mmol/L sucrose, 10 mmol/L Tris-HCl, 1 mmol/L EGTA) depending on the enzyme activity assayed. Enzymatic activities for hydroxacyl-Coenzyme A dehydrase, hexokinase, and citrate synthase were determined as previously described.16 Enzymatic activities for carnitine palmitoyl transferase and malonyl-CoA decarboxylase enzymatic activity determination were also previously described elsewhere.17

Analysis of mRNA Accumulation by Quantitative Reverse Transcription-Polymerase Chain Reaction
The analysis of LV mRNA levels by quantitative reverse transcription-polymerase chain reaction has been described in details elsewhere.18

Immunoblotting
Crude LV homogenates were separated by SDS-PAGE. Immunoblotting was performed as described elsewhere.17 Membranes were hybridized with the indicated primary antibodies. All primary antibodies against the phosphorylated or the total form of the different signaling proteins (Erk 1/2, p38, Jnk, Akt, or protein kinase B) were used at a 1:1000 dilution and were purchased from Cell Signaling Technology (Beverly, MA).

Statistical Analysis
Results are presented as mean±SEM unless specified otherwise. Comparison of variance between groups was performed using Bartlett and Brown–Forsythe tests. Data were log-transformed when variances were different between groups to equalize them. Intergroup comparisons were done using 1-way ANOVA and Tukey post-test or Student t test. Survival was analyzed by standard Kaplan–Meier analysis with log-rank test. Statistical significance was set at a P<0.05. Data and statistical analysis were performed using Graph Pad Prism version 6.02 for Windows, Graph Pad Software (San Diego CA).

Results
Survival Data and Animal Characteristics
Cpt was well-tolerated by all animals. Figure 1 shows the survival curves of untreated (AR) or Cpt-treated (AR-Cpt)
animals over a period of 210 days. All sham-operated animals were alive at the end of the protocol (not shown). Ninety-five percent of animals treated with Cpt were alive after 7 months compared with only 68% in the untreated group. No animals in either groups developed signs of overt HF defined as excessive weight gain, labored breathing, peripheral edema, or decrease of fractional shortening <30% at echo. Most deaths were unexpected based on previous day examination and were unwitnessed because they occurred overnight.

LV Remodeling, Function, and Hypertrophy
After 7 months, surviving animals underwent a final echocardiogram and their hearts were harvested subsequently for tissue analysis. Several randomly chosen animals also underwent a µPET scan for more precise LV volume and function measurements (Figure 2) as well as myocardial metabolism evaluation (see next sections). AR resulted in severe LV hypertrophy and dilatation as demonstrated by the increased total heart and LV weight as well as end-diastolic and end-systolic diameters (Table). Cpt significantly decreased LV hypertrophy, dilatation, and systolic dysfunction. The echocardiographic findings were corroborated by the µPET measurements of LV end-diastolic volume, end-systolic volume, and ejection fraction (Figure 2).

Markers of Hypertrophy and Extracellular Matrix Remodeling
As expected, ANP and BNP gene expression were elevated in AR animals. Cpt treatment reduced ANP mRNA levels in AR animals but not those of BNP (Figure 3B). The relative gene expression of both the α and β forms of myosin heavy chains was modified in untreated AR animals in which the α/β ratio was strongly reduced. Cpt treatment normalized the expression of both myosin heavy chains in AR rats (Figure 3B). The mRNA levels of collagen 1, 3, and fibronectin were also measured in the LV samples. Figure 3C clearly shows that AR significantly increased the expression of collagen 1, 3, and fibronectin. Cpt treatment significantly decreased this overexpression with a return to close to normal values for collagen 1 expression.

Myocardial Energetic Metabolism and Markers
Free fatty acid uptake was evaluated by µPET quantification as shown in Figure 4. LV fatty acid uptake was reduced in AR animals compared with controls. These changes in fatty acid uptake were predominant in the LV lateral wall. Cpt treatment normalized this parameter in AR animals.

These findings were corroborated by the evaluation of various LV energy metabolism markers measured directly in myocardial samples (Figure 5). The carnitine palmitoyl trans-ferase activity which mediates the entry of fatty acids into the mitochondria was reduced in the LV of AR animals. Captopril treatment normalized these activity levels. Fatty acid oxidation (FAO) capacity was impaired in the LV of AR rats as illustrated by the decreased hydroxyacyl-Coenzyme A dehy-drogenase enzymatic activity (Figure 5A). Cpt restored this

Table. Animal Characteristics and Echocardiographic Data in Surviving Animals

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Sham</th>
<th>AR</th>
<th>Ar-Cpt</th>
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<tr>
<td>Heart, mg</td>
<td>1555±40</td>
<td>2311±83†</td>
<td>1799±51*§</td>
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<td>12.3±0.1†</td>
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<td>FS %</td>
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<td>35±2†</td>
<td>36±1†</td>
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<td>Lungs, mg</td>
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<td>2903±141</td>
<td>2659±110</td>
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AR indicates aortic valve regurgitation controls; AR-Cpt, AR treated with captopril; EDD, end-diastolic diameter; ESD, end-systolic diameter; FS, fractional shortening; HR: heart rate; ind, indexed; LV, left ventricle; na, not applicable; and SW, septal wall thickness. Values are expressed as mean±SEM. Number of animals per group indicated in parenthesis. Echo measurements obtained under inhaled 1.5% isoflurane anesthesia in surviving animals.

*P<0.05 vs sham animals.
†P<0.001 vs sham animals.
‡P<0.01 vs untreated AR animals.
§P<0.001 vs untreated AR animals.
parameter to normal levels. Malonyl-CoA is an inhibitor of carnitine palmitoyl transferase activity and thus of FAO. The malonyl-CoA decarboxylase is responsible for the conversion of malonyl-CoA to acetyl-CoA. Malonyl-CoA decarboxylase activity was reduced in untreated AR animals and captopril treatment normalized activity levels. FAT/CD36 is the cell membrane transporter implicated in the entry of fatty acids inside the cell. FAT/CD36 gene expression was reduced in AR LVs and captopril treatment helped maintain normal expression (Figure 5B). PPARα mRNA levels, a transcription factor implicated in the control of various FAO genes (Figure 5B) as well as those of PGC1α, a PPARα coactivator, were reduced in AR and captopril normalized their levels.

Conversely, the first step of glycolysis, catalyzed by hexokinase, was increased in AR rats, but Cpt returned this parameter to normal, whereas mRNA levels of pyruvate dehydrogenase that is responsible for the conversion of pyruvate to acetyl-CoA were reduced in AR animals but not in the Cpt group (Figure 5C). We measured citrate synthase activity and aconitase 2 gene expression at the mitochondrial level (Figure 5D). In both AR and Cpt-treated AR rats, citrate synthase enzymatic activity was slightly reduced. Aconitase 2 mRNA levels were reduced by AR, but Cpt partially restored these levels to normal.

**G-Protein Receptor Kinase 5 Expression**

The angiotensin II type 1 receptor is one of the possible substrates for the G-protein receptor kinase 5 (GRK5). GRK5

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**Figure 3.** Evaluation by real-time quantitative reverse transcription-polymerase chain reaction of the left ventricular (LV) mRNA levels of genes related to LV hypertrophy (A and B) and extracellular matrix remodeling (C). Results are reported in arbitrary units (AU) as means±SEM (n=12 per group). **P<0.01 and ***P<0.001 between sham and AR groups. §§§P<0.01 and §§§P<0.001 vs untreated AR group. Sham (sham-operated animals) group mRNA levels were normalized to 1. ANP indicates atrial natriuretic peptide; AR, aortic valve regurgitation controls; AR-Cpt, AR treated with captopril; BNP, brain natriuretic peptide; Col1, collagen 1; Col3, collagen 111; Fn, fibronectin; αMHC, myosin heavy chain α; βMHC, myosin heavy chain β; PLB, phospholamban; and SERCA2a, sarcoplasmic reticulum Ca2+-ATPase.

**Figure 4.** Myocardial fatty acid (A) uptake in the left ventricular (LV) myocardium of AR rats as evaluated by μ positron emission tomography compared with sham animals. Total (B) and regional (C) LV fatty acid uptake were estimated in sham, AR, and AR-Cpt animals. Fluorothioheptadecanoic acid uptake was evaluated as described in the Materials and Methods section (n=4 per group) and are expressed as the means±SEM. *P<0.05 vs sham and AR groups. §§P<0.05 vs untreated AR group. AR indicates aortic valve regurgitation controls; AR-Cpt, AR treated with captopril; and Ctrl, control.
expression has been shown to be up-regulated in heart diseases. In Figure 5E, it is illustrated the GRK5 mRNA levels in the LV of AR rats treated or untreated with Cpt. AR rats expressed higher levels of GRK5 compared with controls, and Cpt treatment was able to almost normalize these levels.

Prohypertrophic Pathways and the Activation of Akt
Some classical prohypertrophic pathways were also evaluated. AR did not affect the expression of Erk1/2, p38, or Jnk and neither did Cpt treatment. However, AR significantly increased the expression of Akt-phosphorylated Akt ratio, whereas Cpt significantly prevented this overexpression. The expression of AMPK was not affected by AR but tended to be decreased by the administration of Cpt (Figure 6).

Discussion
The main and most important finding of this study is the first demonstration that ACEI Cpt improves survival in rats with pure severe aortic valve regurgitation. Our findings also confirm our previous observations of the benefits of Cpt in AR.

The controversy regarding the efficacy of vasodilators, including ACEI in the treatment of AR, is far from resolved. Recently, a meta-analysis of all the randomized clinical trials that evaluated vasodilators in AR showed that the evidence points toward the efficacy of vasodilators although a wide discrepancy exists between the trials’ design and results. ACEIs were found almost always favorable in terms of protection against LV dilatation and loss of ejection fraction. The authors, nevertheless, conclude that a large prospective trial remains necessary to confirm their findings considering the paucity of data.

It is also noteworthy that clinical outcome, including survival, has never been properly evaluated in most of the clinical trials published so far mostly because of their lack of statistical power. The most recent clinical trial from Evangelista et al evaluating enalapril failed again to show or even suggest benefits in the drug-treated group. Although it seems logical to assume that clinical outcome will parallel the benefits on LV remodeling and ejection fraction, the proof remains to be obtained. Despite its pitfalls, our animal model has the advantage of being controlled and without any confounding factors. A 7-month follow-up may reflect the subacute period in humans, and it does enclose a true chronic phase in rats because we have previously shown in a paper characterizing this animal model. Our results show a clear effect on LV dilatation, hypertrophy, systolic function, myocardial metabolism, and more importantly on survival. These results provide support for the need to reevaluate ACEI in humans with AR in a large prospective clinical trial.
We report that Cpt has a significant impact on myocardial energy metabolism. To our knowledge, no other study has evaluated the metabolic response of the heart to severe volume overload caused by AR and the effects of a drug treatment on this parameter. Whether the improvement in myocardial metabolism is the cause or the effect of the reduction of LV dilation, hypertrophy, and improved systolic function remains unknown and will need to be studied in other protocols.

In our study, Cpt reduced LV dilation and volume and, consequently, wall stress. The severity of AR remained the same because AR is the result of an induced mechanical defect. Because the aortic valve lesion remained similar between both the untreated and the Cpt-treated group, the LV volume overload was not eliminated by the Cpt treatment. Nevertheless, Cpt was associated with lower ANP mRNA levels and a normal profile of MHC isoforms gene expression. The same was true for the expression of several components of the extracellular matrix. Although interstitial fibrosis is not an early feature of this animal model of eccentric LV remodeling, significant accumulation of collagen is present in later stages (≥6 months). Our results suggest that the dilated hearts of Cpt-treated AR animals tolerated the abnormal hemodynamic overload and maintained a near normal myocardial metabolic profile. We previously showed that blood pressure in AR animals treated with Cpt is only slightly reduced and had similar findings in this protocol.6 This suggests that the hemodynamic contribution to the benefits of angiotensin-converting enzyme (ACE) inhibition although present is not the main and only factor involved.6

The previously reported shift toward glucose use by the myocardium in compensated hypertrophy was not observed in our Cpt-treated AR rats. We have recently reported this shift in substrate uptake in 8-week AR animals.23 We observed that myocardial glucose uptake was increased, whereas fatty acid was reduced in those animals. The overall myocardial oxidative capacity remained unchanged. In this study, our data suggest similar findings after 7 months. Survivor AR rats did not show clinical signs of HF at the end of this study. Lungs weights were similar between groups arguing against the presence of subclinical pulmonary edema. An energy profile reminiscent of HF was not present in any of the AR animals, suggesting that the left ventricular hypertrophy state was still compensated. On a clinical standpoint, it would be advantageous to lessen LV dilation, extracellular matrix remodeling, and maintain a normal energy substrate use for as long as possible.

Blocking angiotensin II (AngII) formation using ACE inhibition has shown its benefits in cardiac hypertrophy for a long time.26,27 AngII plays a major role in the development of hypertrophy and fibrosis. AngII increases norepinephrine release, the rate and force of cardiac contraction, and myocardial cell growth by its interaction with angiotensin II receptor type 1.27 Its impact on myocardial metabolism is not well-understood. Depending on the model studied, AngII is associated either with increased or decreased glucose use. Short-term AngII administration to cultured rat neonatal cardiac myocytes leads to increased glucose uptake, whereas fatty acid uptake remains unchanged.23 Cardiac targeted overexpression of angiotensinogen has been shown to decrease FAO in HF mice but not in those displaying a compensated form of heart hypertrophy.25 A long-term treatment with AngII reduced FAO26 in cultured rat neonatal cardiomyocytes. In our model, we cannot conclude whether the observed effects of ACE inhibition on energy metabolism were the cause or an effect of the reduction of hypertrophy. Considering that ACE inhibition did
not completely prevent hypertrophy and that the LV still had to cope with volume overload, the energetic demand of the myocardium was still probably increased. We observed that Akt activation in the AR LV was reversed by ACE inhibition. The Akt signaling pathway is an interesting target because it is both prohypertrophic and stimulator of glucose use by the cell. Because the Akt cascade can be activated by various stimuli, including integrins (mechanical cellular stretch) and G-protein–coupled receptors, such as the angiotensin II receptor type I, it is possible that effects of Cpt in limiting the hypertrophic response may also have contributed to a reduced use of glucose. Moreover, Akt activation is linked to the down-regulation of PPARα and PGC1α, both stimulator of FAO. We have recently shown in the same animal model that LV remodeling can be influenced by diet manipulation and by drugs, such as metformin and fenofibrate, which have significant metabolic effects, whereas lacking any hemodynamic effects. This suggests that manipulating myocardial metabolism without hemodynamic effects can impact LV remodeling in AR.

GRK5 expression was increased in the LV of AR rats as previously observed. G-protein–coupled receptor–independent actions of GRK5 have recently been reported. GRK5 accumulates in the nucleus of myocytes after a hypertrophic stimulus. It enhances Gq-mediated cellular growth via its capacity to phosphorylate the histone deacetylase 5 kinase leading to MEF2 repression, a transcription factor regulating cardiac myocyte growth. GRK5 may, therefore, be another molecular target to study in our animal model of AR.

In summary, we report for the first time that a long-term treatment with Cpt decreases sudden death in a rat model of chronic AR. These benefits on survival were accompanied in surviving animals with decreased LV hypertrophy and improved myocardial energetics. The mechanisms involved are obviously complex and further studies will be necessary to better understand the response of the myocardium to volume overload in the context of ACE inhibition.

Disclosures
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References


**CLINICAL PERSPECTIVE**

Chronic, severe aortic valve regurgitation remains a therapeutic enigma for clinicians. Various vasodilators have been tested to treat the consequences of this valve lesion in an attempt to protect the left ventricle against volume overload, but their efficacy remains controversial, and their use is not currently recommended on the basis of findings of past clinical trials. When such controversies arise, reassessment in translational models may help to better understand the problem and propose new therapeutic targets and directions. This paper evaluated the efficacy of the angiotensin-converting enzyme inhibitor captopril in an animal model of pure aortic valve regurgitation and showed for the first time a benefit in survival. The data also suggest a favorable effect of captopril on myocardial energetic metabolism and potential new molecular targets to investigate in AR treatment.
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