Effects of Early, Late, and Long-term Nonselective β-Blockade on Left Ventricular Remodeling, Function, and Survival in Chronic Organic Mitral Regurgitation

Min Pu, MD, PhD; Zhaohui Gao, MD; Daniel K. Pu, MD; William R. Davidson Jr, MD

Background—Mitral regurgitation (MR) produces sympathetic nervous system activation which is detrimental in other causes of heart failure. However, whether β-blockade is beneficial in MR has not been determined.

Methods and Results—Eighty-seven rats with significant organic MR were randomized to the β-blockade group (n=43) or the control group (n=44). Carvedilol was started in week 2 post MR induction and given for 23 to 35 weeks in the β-blockade group. Echocardiography was performed at baseline and at weeks 2, 6, 12, 24, 30, and 36 after MR induction. After 23 weeks of β-blockade, heart rates were significantly reduced by carvedilol (308±25 versus 351±31 beats per minute; P<0.001). Left ventricular end-diastolic (2.2±0.7 versus 1.59±0.6 mL; P<0.001), end-systolic volumes (0.72±0.42 versus 0.40±0.19 mL; P<0.001), and mass index (2.40±0.55 versus 2.06±0.62 g/kg; P<0.001) were significantly higher, and left ventricular fraction shortening (33±7% versus 38±7%; P<0.001) and ejection fraction (69±11% versus 75±7%; P<0.001) were significantly lower in the β-blockade group than in the control group. Systolic blood pressure was lower in the β-blockade group than in the control group (114±10 versus 93±12 mm Hg; P<0.005). Survival probability was significantly lower in the early β-blockade group than in the control group (88% versus 96%; P=0.03).

Conclusions—Early and long-term nonselective β-blockade was associated with adverse left ventricular remodeling, systolic dysfunction, and a reduction in survival in the experimental rat model of organic MR. (Circ Heart Fail. 2013;6:756-762.)

Key Words: β-blocker ■ left ventricular function ■ left ventricular remodeling ■ mitral regurgitation

There are >500,000 patients experiencing moderate to severe valvular regurgitation in the United States. The Framingham Study noted that the prevalence of mitral regurgitation (MR) increases 1.3-fold with each decade of life. It is anticipated that the prevalence of MR will increase even further because of the rapidly growing aged population in the United States and worldwide.

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Early surgical intervention in chronic organic MR has been advocated in recent years, especially when mitral valve repair seems feasible. However, most of the patients with chronic MR do not undergo surgical intervention. For example, there are 500,000 hospital discharges with the diagnosis of mitral valve disease each year in the United States, but only ≈18,000 patients (3.6%) undergo mitral valve surgery annually. There is an on-going debate on optimal management strategy for asymptomatic patients with chronic MR and normal left ventricular (LV) function, particularly when mitral valve repair is not feasible or significant comorbidities are present. Therefore, clinicians have long been interested in finding nonsurgical therapies for chronic MR. Traditional drugs for the treatment of congestive heart failure, including vasodilators and angiotensin-converting enzyme inhibitors, have been tested. Although these medications may have acute favorable hemodynamic effects in MR, they have not shown promising results in limited long-term studies. A small clinical observational study showed that carvedilol improved LV remodeling and reduced MR in patients with congestive heart failure caused by nonvalvular heart disease (ischemic heart disease or nonischemic cardiomyopathy). A retrospective study showed β1-blockade could prolong survival in MR, although this study was significantly limited by many confounding factors. Because β-blocker therapy is beneficial for heart failure not caused by MR, it is reasonable to hypothesize that β-blockade could have beneficial effects in congestive heart failure caused by chronic organic MR. In particular, the benefits might be more pronounced if β-blockade was started early, before the development of irreversible LV dysfunction. Animal studies have shown that β-blockade could improve LV systolic function in chronic MR. Recent clinical studies have also shown that β1-blockade may improve LV systolic function in chronic organic MR, but a beneficial effect...
on LV remodeling is uncertain.12,13 There have been no studies yet demonstrating that β-blockade improves LV remodeling in chronic organic MR. Furthermore, a dissociation between adverse LV remodeling and improvement in cardiac myocyte contractility in experimental MR treated with β-blockers has been reported.14 This dissociation creates a possible pathophysiological contradiction because adverse LV remodeling is often associated with LV dysfunction and poor long-term outcome in all forms of congestive heart failure. Therefore, it is important to determine whether beneficial effects of β-blockade could be demonstrated if chronic organic MR was treated in the early stages before the development of LV dysfunction and if treatment is long-term. It is also imperative to determine whether LV remodeling associated with β-blocker therapy could ultimately have a negative impact on LV function in chronic organic MR or if the early improvement in LV function and myocardial contractility observed in prior studies could lead to improvement in LV remodeling if treatment was initiated early and long-term.

To clarify this important issue, we performed a prospective study to determine the effects of early, late, and long-term β-blockade on LV remodeling, systolic function, and survival in experimental chronic MR. The study design had the following unique characteristics: (1) the study used a unique rat model of chronic MR developed in our laboratory,15 allowing us to use a large numbers of animals to test the hypothesis; (2) carvedilol (a nonselective β-adrenergic blocking agent with α1-blocking activity) was administered early before the development of LV systolic dysfunction; and (3) a long-term treatment strategy was applied.

Methods

Rat Model of MR

The study protocol was approved by the Institution’s Animal Care and Use Committee of the Pennsylvania State University College of Medicine (assurance number A3045-01). The study was performed according to the guidelines of the American Society of Physiology. The study used Sprague-Dawley rats (180–339 g). MR was induced using techniques which were previously described.16 An intracardiac echocardiographic catheter (Acuson/Siemens Corporation, Mountain View, CA) was used to obtain transesophageal echocardiographic images to assess the severity of MR.17 LV mass was considered significant if a regurgitant jet area occupied >40% of left atrial area with a visible MR vena contracta or a reversed pulmonary venous flow pattern.

β-Blockade

A total of 114 rats underwent MR induction surgery. Eighty-seven rats survived perioperatively (7 days post surgery) with significant MR. Among them, 43 rats were randomized into the β-blockade group and 44 rats were randomized into the control group in the early stage of MR. Carvedilol (GlaxoSmithKline) was added to the rat chow (1200 parts per million in a Harlan Teklad Global Diet).18 The study was performed using techniques which were previously described.16 An intracardiac echocardiographic catheter (Acuson/Siemens Corporation, Mountain View, CA) was used to obtain transesophageal echocardiographic images to assess the severity of MR.17 Carvedilol treatment was applied.

Echocardiography

Two-dimensional (2D), color Doppler, and pulsed-wave Doppler imaging were performed using a special probe for small animals (14 MHz, Acuson/Siemens Corporation, Mountain View, CA). Parasternal long- and short-axis 2D views were recorded as previously described.19 M-mode images were obtained at the level of the chordae tendineae of the mitral valve in the short-axis view under the guidance of 2D imaging. To assess the time course of LV remodeling, transthoracic echocardiography was performed at baseline before MR induction, and at weeks 2, 6, 12, 24, 30, and 36 after MR induction. All images were recorded digitally. Echocardiography parameters were measured blinded to the assignment of the β-blockade and non-β-blockade groups. Measurements were averaged for 3 cardiac cycles.

Assessment of LV Remodeling

LV end-diastolic dimension (LVEDD), LV end-systolic dimension (LVESD), interventricular septal (IVS) thickness, and LV posterior wall thickness (PW) were measured from M-mode echocardiography as recommended by the American Society of Echocardiography.20 LVEDD/wall thickness ratio was calculated as (LVEDD/2)/LVPW, and LV mass was calculated as3

\[ \text{LV mass} = 1.04 \times \left( \frac{\text{LVEDD} + \text{PW}}{\text{IVS}} \right)^{3/2} \times 0.8 + 0.14 \]

LV mass/weight index was calculated as LV mass divided by body weight (kilogram). LV end-diastolic volume (LVEDV) and LVESV were calculated as LVEDV=LVESV×π/3 and LVESV=LVESD×π/3, respectively.21 LV volume/mass ratio was calculated as LV volume divided by LV mass.

Assessment of Systolic Function

LV fractional shortening (LVFS), LV ejection fraction (LVEF), LVESD, and LVESV were measured for the assessment of LV systolic function. LVFS was calculated as LVFS=(LVEDV–LVESD)/LVEDV×100%. LVEF was calculated as LVEF=(LVEDV–LVESV)/LVEDV×100%.

Heart Rate and Blood Pressure Measurement

Heart rates were measured from electrocardiographic monitoring during the echocardiography study. Invasive blood pressure measurements were performed at weeks 36 to 56 (46±7 weeks) post MR induction in 13 rats in the late control group, 13 rats in the late β-blockade group, 15 rats in the β-blockade withdrawn group, and 9 rats in the long-term β-blockade group. Briefly, the carotid artery was isolated and a Millar catheter was inserted into the carotid artery and advanced into the ascending aorta to record blood pressure. Blood pressure data were transferred to PowerLab (AD Instrument, CO). Systolic and diastolic pressures were measured offline blinded to the assignment of the β-blockade and non-β-blockade groups.

Statistical Analysis

All data are expressed as mean±SD. Measurements of LV volumes, mass, and function were obtained at week 2 before the randomization and then at weeks 6, 12, and 24. Repeated measures ANCOVA was used to test the overall main effect of the treatment on the follow-up measures using the baseline and week 2 as covariates. Group by time interaction was also tested to see whether the effect was similar at each of the 3 follow-up times. Because there were some group by week interactions, post hoc comparisons between the groups at the follow-up weeks were performed at the individual follow-up times. Kaplan–Meier curves were used to estimate the survival probabilities and the curves were compared using the log-rank test.
Results

Effect of Early β-Blockade on Heart Rate
Changes in heart rates in the early β-blockade and control group are illustrated in Table 1. There were no significant differences in heart rates between the MR control group and β-blockade group at baseline and week 2 post MR induction before carvedilol was started. However, there was a significant decrease in heart rates in the β-blockade group at weeks 6, 12, and 24. Heart rates were also significantly lower in the late β-blockade group than in the late control group in weeks 30 (311±35 versus 334±35 beats per minute; *P*<0.001) and 36 (307±43 versus 341±29 beats per minute; *P*<0.001). Heart rates increased from 302±21 to 343±34 beats per minute at week 30 to 342±30 beats per minute at week 36 in the β-blockade withdrawn group, which were significantly higher than in the long-term β-blockade group (309±32 beats per minute at week 30; *P*<0.001 and 309±30 beats per minute at week 36; *P*<0.001).

Effects of β-Blockade on Blood Pressure
Table 2 shows the invasive blood pressure measurements. Systolic and diastolic blood pressures were significantly lower in the late and long-term β-blockade groups than in the late control group and β-blockade withdrawn group. There was no statistical difference in systolic and diastolic blood pressures between the late control group and the β-blockade withdrawn group indicating that carvedilol lowers blood pressure in rat models of chronic MR.

Effect of Early β-Blockade on LV Remodeling and Function
Table 3 shows effect of β-blockade on LV volume, mass, and function. There were no significant differences in LV end-diastolic and LVESV between the β-blockade and control group at baseline (before MR induction) and at week 2 before the administration of carvedilol. Increases in LV volumes were noted in both groups at week 2 because of volume overload caused by MR. LV volumes and mass increased more significantly and rapidly in the β-blockade group (weeks 6, 12, and 24). LVESV, LVEF, and LVFS were used as indices of LV systolic function. There were no significant differences in LVFS and LVEF at baseline and at week 2 between the control and the β-blockade groups before β-blockade, LVFS, and LVEF increased initially at week 2, consistent with an early compensatory hyperdynamic LV because of MR volume overload. However, LVESV was significantly higher, and LVFS and LVEF were significantly lower in the β-blockade group than in the control group at weeks 6, 12, and 24 after β-blocker treatment. Decreases in LVFS and LVEF were more pronounced in the β-blockade group than in the control group, although gradual decreases in LVFS and LVEF were also seen in the control group because of impairment of LV systolic function caused by chronic volume overload.

Effects of Late β-Blockade on LV Remodeling and Function
After echocardiography was performed at week 24 post MR induction, rats in the early control group were rerandomized into the late control group (n=20) and late β-blockade group (n=22). There were no significant differences in the heart rates, LV dimensions, volume, LVFS, and LVEF between the late control and late β-blockade groups before late β-blocker treatment. However, heart rates were significantly lower, LV dimensions and volumes were larger, and LVFS and LVEF were lower in the late-β blockade group than in the late control group (Table 4).

Table 1. Effect of Carvedilol on Heart Rate

<table>
<thead>
<tr>
<th>Heart Rate, beats per minute</th>
<th>Baseline</th>
<th>Week 2</th>
<th>Week 6</th>
<th>Week 12</th>
<th>Week 24</th>
<th>Group Main Effect</th>
<th>Group by Week Interaction</th>
</tr>
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<tbody>
<tr>
<td>Control</td>
<td>370±37</td>
<td>388±34</td>
<td>359±48</td>
<td>352±35</td>
<td>351±31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockade</td>
<td>365±37</td>
<td>379±32</td>
<td>317±29</td>
<td>315±22</td>
<td>308±25</td>
<td></td>
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<tr>
<td><em>P</em> values</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
<td>0.68</td>
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</table>

There are no differences in heart rate between the control and β-blockade groups at baseline and week 2 (*P* value >0.05).
Effect of β-Blockade on Survival

Figure 2 presents the Kaplan–Meier survival curves in the control and β-blockade groups during the period of early β-blocker treatment. All rat deaths occurred 17 weeks post MR induction when LVEF and LVFS had significantly decreased with substantial LV remodeling in both the control and the β-blockade groups. The survival probability was 96% (95% confidence interval, 90%–100%) in the control group and 88% (95% confidence interval, 79%–98%; *P* =0.03) in the β-blockade group. During the period of late β-blocker treatment, there were 1 death (n=19, 5%) in the β-blockade withdrawn group, 3 deaths (n=20, 15%) in the late control group, 5 deaths (n=22, 23%) in the late β-blockade group, and 6 deaths (n=19, 32%) in the long-term β-blockade group. Long-term and late β-blockade did not show to prolong survival.

Discussion

In humans with chronic organic MR, increases in LVESD and LVESV indicate adverse LV remodeling which is associated with a poor prognosis. These measures provide threshold values indicating a need for valve surgery.3 Because nonselective β-blockade is effective at preventing and reversing adverse LV remodeling in patients with ischemic and dilated cardiomyopathies, it has been suggested that it might be of benefit in organic MR. Prior studies showed that β-blockade improved LV function in canine models of chronic organic MR9 and in patients with degenerative mitral valve disease in pilot clinical studies.13 However, the effect of β-blockade on LV remodeling in chronic organic MR is uncertain and seems to be different from that on LV function. No prior studies have demonstrated beneficial effects of β-blockade on LV remodeling in organic MR.12,13 Therefore, the dissociation between a reported improvement in LV function (LVEF) and a lack of effect on LV remodeling in chronic organic MR treated with β-blockers requires further investigation.

β-Blockade in Chronic Organic MR

The sympathetic nervous system may be activated in experimental MR9 and in patients with chronic MR and LV dysfunction.23 Carabello et al10 reported that β1-blockade restored impaired LV systolic function in a canine model of chronic organic MR with congestive heart failure. This beneficial

<table>
<thead>
<tr>
<th>Table 2. Effect of Carvedilol on Blood Pressure</th>
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<tr>
<td>Blood Pressure</td>
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<td>----------------</td>
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<tr>
<td>Systolic BP, mm Hg</td>
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<td>Diastolic BP, mm Hg</td>
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</table>

There were no statistical differences in systolic and diastolic blood pressures between the control and β-blockade withdrawn groups. BB indicates β-blockade; and BP, blood pressure.

Comparison between the control and the late β-blockade groups, and between the control and long-term β-blockade groups: *P*<0.01 and **P*<0.005.

<table>
<thead>
<tr>
<th>Table 3. Effects of Early β-Blockade on Left Ventricular Remodeling and Function</th>
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<tr>
<td></td>
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<tr>
<td>LVEDV, mL</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>β-Blockade</td>
</tr>
<tr>
<td>LVESV, mL</td>
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<tr>
<td>LV mass index, g/kg</td>
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<tr>
<td>LVFS, %</td>
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<tr>
<td>LVEF, %</td>
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</table>

There are no differences in LVEDV, LVESV, LV mass index, LVFS, and LVEF between the control and β-blockade groups at baseline and week 2 (all *P* values >0.05). LV indicates left ventricular; LVEDV, LV end-diastolic volume; LVEF, left ventricular ejection fraction; LVFS, LV fractional shortening; and LVESV, LV end-systolic volume.
Effect on LV systolic function seemed to result from the bradycardia induced by β-blockade because it was not present when bradycardia was prevented by pacing. Effect of β1-selective blockade on hemodynamics in chronic organic MR includes decreases in heart rate and blood pressure and increases in LV end-diastolic and LVESV. Increase in forward stroke volume was associated with a reduction in blood pressure.

This study, however, showed that nonselective β-blockade had no beneficial effect on LV remodeling in a rat model of chronic organic MR. In contrast, β-blockade seemed to accelerate the progression of LV remodeling and was associated with worsened LV function with long-term treatment. Although heart rates were significantly reduced in the β-blockade groups, there was no survival benefit. Our findings are consistent with a previous experimental study that β-blockade could cause significant increases in LV dimensions and volumes.

Nonbeneficial effect of β-blockade on LV remodeling was also observed in patients with organic MR and normal LV function. Furthermore, in a prior study of volume overload caused by aortocaval shunt, LV weight was significantly greater in rats treated with a β-blocker than those without β-blocker treatment.

These findings suggest that the pathophysiology of LV remodeling caused by primary volume overload, such as organic MR, may be different from other forms of congestive heart failure in which myocardial damage (ischemic heart disease, cardiomyopathy) is the primary insult.

Differences in β-Blockers

In prior studies, β1-adrenergic receptor antagonists (atenolol and metoprolol) were used in the treatment of organic MR. In this study, carvedilol (a nonselective adrenergic receptor antagonist) was used because it has beneficial effects of reducing heart rate and afterload, as well as improving myocardial contractility and LVEF, in congestive heart failure.

Similar to previous findings, heart rate and blood pressure decreased in the β-blockade group in the current study. Rats with organic MR tolerated carvedilol well at the early stages of MR. There were no deaths in the first 17 weeks after carvedilol treatment, which excludes the possibility of catastrophic deterioration of hemodynamics, such as cardiogenic shock, because of the combination of α1- and β1-receptor blockade. Recent literature shows that α1-receptors may have protective effects in congestive heart failure and blockade of α1-receptors could have deleterious effects. Whether the adverse effect of carvedilol on LV remodeling and function in chronic organic MR is related to the blockade of α1-adrenergic receptor and β2-receptor is unknown. This is clinically relevant because several prior studies have called for clinical trials of β-blocker treatment in chronic organic MR.

Future Studies

The inability to demonstrate overall beneficial effect of neurohormonal antagonists (angiotensin-converting enzyme inhibition) or β-blockers did not conflict with the recent American College of Cardiology/American Heart Association guidelines that do not support a routine use of these medications in chronic organic MR.”

<table>
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<th>Table 4. Effect of Late β-Blockade on Left Ventricular Remodeling and Function</th>
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<tr>
<td>Week 24</td>
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<tr>
<td>Late Control (n=20)</td>
</tr>
<tr>
<td>LVEDD, cm</td>
</tr>
<tr>
<td>LVESD, cm</td>
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<tr>
<td>LVEDV, mL</td>
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<tr>
<td>LVESV, mL</td>
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<td>LVFS, %</td>
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<tr>
<td>LVEF</td>
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<tr>
<td>Heart rate, beats per minute</td>
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</table>

BB indicates β-blockade; LVEDD, LV end-diastolic dimension; LVEDV, LV end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, LV end-systolic dimension; LVESV, LV end-systolic volume; and LVFS, LV fractional shortening.

Comparison between the late control group and the late β-blockade group: *P<0.05; and **P<0.001.
inhibitor, angiotensin II receptor blocker, and β-blocker) on LV remodeling in chronic organic MR suggests the pathophysiology of congestive heart failure caused by chronic organic MR may be different from nonorganic MR because of ischemic heart disease or cardiomyopathy. A possible explanation for the detrimental effects of early β-blockade in chronic organic MR may be that β-blockade depresses LV systolic function and myocardial contractility, which is normally maintained by the sympathetic nervous system. Long-term depression of myocardial contractility could lead to failure to maintain a normal LVESD in the condition of significant volume overload imposed by severe MR. Dilation of LVESD increases LV wall stress and mechanical stretching of myocytes. This could activate the signaling pathways accelerating the loss of the myocardial extracellular matrix and downregulation of noncollagen extracellular matrix which could lead to LV dilation and adverse remodeling. In the long term, significant LV remodeling is associated with deterioration of LV function. The early study from Cooper’s group demonstrated that most of the deleterious effects of chronic organic MR seemed to be because of a combination of myofibrillar loss and failure of compensatory hypertrophy. The recent molecular study from Dell’Italia et al confirmed that myocardial extracellular matrix loss and LV remodeling were more significant in canine models of organic MR treated with β-blockers. Therefore, studies of interventions to prevent LV remodeling and reduce extracellular matrix loss may be important for managing this unique pathophysiology.

Limitations
Although rat models of cardiovascular disease have been successfully used to test multiple medical therapies, a rat model of chronic organic MR is relatively new. In addition, MR is acutely and mechanically induced in all animal models of organic MR. Progression of LV remodeling, therefore, may be different from patients with degenerative mitral valve disease in which the severity of MR often increases gradually unless rupture of the chordae tendineae of the mitral valve occurs. Although this study evaluated the effect of β-blockade in acute and chronic stages of organic MR by designating the early and late β-blockade groups, one should not extrapolate experimental results to clinical patients. Adverse effects of nonselective β-blockade on LV remodeling, function, and survival in the rat model of chronic MR warrant further investigation in large animal models or humans. The current experimental study provides additional information to investigators before the initiation of a clinical trial of β-blocker therapy for chronic organic MR.

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Disclosures
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decreased survival. This study demonstrates the importance of LV remodeling in chronic organic MR and provides clinicians with carvedilol in heart failure. Circ Heart Fail. 2009;2:189–196.


**CLINICAL PERSPECTIVE**

Mitril regufituation (MR) is common in clinical practice. For functional MR, treatment of primary myocardial dysfunction with β-blockers is beneficial. For chronic organic MR (degenerative valvular disease), left ventricular (LV) function is normal initially. Many patients with moderate to severe chronic MR are asymptomatic for a long period of time, while LV remodeling occurs. The use of early β-blockade to delay LV remodeling and improve LV function have been studied in chronic organic MR, and clinical trials have been proposed. However, the beneficial effect of early and long-term β-blockade on LV remodeling in chronic organic MR is uncertain. In this study, we examined the effects of a nonselective β-blocker (carvedilol) on LV remodeling, function, and survival in a rat model of organic MR. We observed that LV mass and volumes were significantly higher, and LV ejection fraction and fractional shortening were significantly lower in the β-blockade group than in the non-β-blockade group. Early and long-term β-blockade accelerated LV dilatation and LV dysfunction with decreased survival. This study demonstrates the importance of LV remodeling in chronic organic MR and provides clinicians additional information regarding the use of early and long-term β-blocker therapy for chronic MR before randomized clinical trials. Further studies are needed to determine (1) whether differences in pharmacological activity (β1-selective versus nonselective blockade) or the unique pathophysiology of organic MR is responsible for the adverse effect of β-blockade on LV remodeling; (2) whether early and long-term β-blockade is effective, beneficial, or harmful in chronic organic MR.
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