Impact of chronic lisinopril therapy on left atrial volume versus dimension in chronic organic mitral regurgitation

Graham C Wong MD, Francois Marcotte MD, Lawrence G Rudski MDCM FACC

GC Wong, F Marcotte, LG Rudski. Impact of chronic lisinopril therapy on left atrial volume versus dimension in chronic organic mitral regurgitation. *Can J Cardiol* 2006;22(2):125-129.

BACKGROUND: Chronic mitral regurgitation imparts a volume load on the left atrium (LA). Because this chamber may dilate asymmetrically, changes in left atrial size may be underestimated using standard two-dimensional or M-mode techniques.

METHODS: The effect of lisinopril therapy in the setting of chronic organic mitral regurgitation on LA dimension was studied using standard M-mode techniques and LA volumes using the biplane Simpson's method.

RESULTS: Mitral regurgitant fraction was reduced at one year in the lisinopril group versus the placebo group ($-6.7\pm 3.5\%$ versus $3.5\pm 3.2\%$, respectively; $P<0.05$). Significant reductions in both maximum and minimum LA volumes were seen in the lisinopril group (88 ± 33 mL to 75 ± 23 mL and 46 ± 20 mL to 38 ± 16 mL, respectively; $P<0.01$). This change in LA size was not appreciated when measurements were performed using standard M-mode techniques (from 44.3 ± 6.9 mm to 44.1 ± 7.4 mm; $P=\text{not significant}$). There was no significant relationship between change in LA volume and change in regurgitant fraction or systolic blood pressure. Change in LA volume was moderately correlated with change in left ventricular mass.

CONCLUSIONS: Angiotensin-converting enzyme inhibitor therapy reduces LA volume in the setting of chronic mitral regurgitation. This change in LA size is not apparent when standard M-mode techniques are used. Therefore, a volumetric assessment of atrial size in the setting of chronic mitral regurgitation proved to be superior to standard two-dimensional techniques.

Key Words: ACE inhibitor; Echocardiography; Left atrium; Mitral regurgitation

Mitral regurgitation (MR) is a common valvular lesion that imparts a volume load on the left ventricle (LV) and left atrium (LA). Over time, MR causes an increase in atrial wall stress and an eventual increase in LA size (1). While many physicians treat severe organic MR with afterload reduction, few randomized trials have actually been performed to address this question (2). In the setting of chronic MR, we have previously shown that treatment with the angiotensin-converting enzyme (ACE) inhibitor lisinopril decreases the mitral regurgitant fraction (RF) (3). A reduction in the RF should theoretically decrease the volume load on the LA, thereby reducing LA wall stress and potentially blunting the increase in LA size often seen with chronic MR. However, we found no difference in LA size between the treatment and placebo groups using standard M-mode echocardiographic measurements in the

Les effets de la thérapie au lisinopril chronique sur le volume de l'oreillette gauche par rapport à sa dimension en cas de régurgitation mitrale organique chronique

HISTORIQUE : La régurgitation mitrale chronique confère une charge volumique à l'oreillette gauche (OG). Puisque cette cavité peut se dilater de manière asymétrique, des modifications à la dimension de l'oreillette gauche peuvent être sous-estimées si elles sont évaluées à l'aide des techniques bidimensionnelles ou en mode M standards.

MÉTHODOLOGIE : L'effet de la thérapie au lisinopril en cas de régurgitation mitrale organique chronique sur la dimension de l'OG a été étudiée à l'aide de techniques en mode M et des volumes de l'OG à l'aide de la méthode bidimensionnelle de Simpson.

RÉSULTATS : La fraction de régurgitation mitrale avait diminué au bout d'un an au sein du groupe prenant du lisinopril par rapport à celui prenant un placebo ($-6,7\% \pm 3,5\%$ par rapport à $3,5\% \pm 3,2\%$, respectivement; $P<0,05$). Des réductions significatives des volumes maximaux et minimaux de l'OG s'observaient au sein du groupe prenant du lisinopril (88 ± 33 mL à 75 ± 23 mL et 46 ± 20 mL à 38 ± 16 mL respectivement; $P<0,01$). Cette modification de la dimension de l'OG n'était pas visible lorsque les mesures étaient calculées au moyen des techniques en mode M standards (de $44,3\pm 6,9$ mm à $44,1\pm 7,4$ mm; $P=\text{non significatif}$). On n'a remarqué aucune relation significative entre la modification du volume de l'OG et la modification de la fraction de régurgitation ou la tension artérielle systolique. La modification au volume de l'OG était modérément reliée à la modification de la masse ventriculaire gauche.

CONCLUSIONS : Une thérapie aux inhibiteurs de l'enzyme de conversion de l'angiotensine réduit le volume de l'OG en cas de régurgitation mitrale chronique. Cette modification de la dimension de l'OG n'est pas apparente lorsque les techniques en mode M standards sont utilisées. Par conséquent, il est démontré que l'évaluation volumétrique de la dimension de l'oreillette en cas de régurgitation mitrale chronique est supérieure aux techniques bidimensionnelles standard.

parasternal long axis (PLAX). Although measurements of the LA are most commonly made in the PLAX using M-mode guided by two-dimensional imaging, this technique may be inaccurate in the assessment of LA size (4). Because the LA may expand in three dimensions, changes in LA size may potentially be missed using standard two-dimensional techniques (1).

The measurement of LA volumes (LAVs) may prove to be a superior method of measuring the LA by taking into account its natural ellipsoid shape. Therefore, we employed a volumetric approach to measuring the LA using the biplane Simpson's method. We hypothesized that treatment with the ACE inhibitor lisinopril would result in a reduction of LAVs in patients with MR – an effect that may not be apparent if LA dimensions are measured using only standard M-mode

Division of Cardiology, Sir Mortimer B Davis Jewish General Hospital and McGill University, Montreal, Quebec

Correspondence: Dr Lawrence G Rudski, Division of Cardiology, Sir Mortimer B Davis Jewish General Hospital, Room E-206, 3755 chemin de la Côte Ste Catherine, Montreal, Quebec H3T 1E2. Telephone 514-340-8222 ext 2992, fax 514-340-7534, e-mail lrudski@cardio.jgh.mcgill.ca

Received for publication November 5, 2004. Accepted August 3, 2005

TABLE 1
Left atrial volume (LAV) and dimensions in lisinopril- and placebo-treated patients at baseline and at one year

	Lisinopril			Placebo		
	Baseline	One year	P	Baseline	One year	P
Maximum LAV (mL)	88.3±33	75.3±23	<0.01	88.1±33	91.1±33	NS
Minimum LAV (mL)	46.0±20	37.8±16	<0.01	47.6±28	48.0±24	NS
LA dimension (mm)	44.3±7	44.1±8	NS	45.4±8	46.7±8	NS

NS Not significant

techniques. Additionally, we attempted to relate any change in LAVs with change in mitral regurgitant fraction and change in systolic blood pressure (BP).

METHODS

Patient population

The design and methods of the present study have been previously described (3). All patients gave informed consent, and the protocol was approved by the institutional review committee. Briefly, patients with at least moderate, isolated, organic (predominantly myxomatous) MR and an LV ejection fraction (LVEF) greater than 60% who were in sinus rhythm and taking no cardiovascular medications at the time of enrollment were recruited. Exclusion criteria included clinically documented coronary artery disease, contraindication to ACE inhibitor therapy, abnormal LV function (EF less than 60% by biplane Simpson's method), severe LV dilation (LV end systolic diameter greater than 45 mm) and resting or stress-induced regional wall motion abnormalities. Twenty-three eligible patients were randomly assigned to receive either lisinopril (target dose 20 mg/day) or placebo, and were followed for one year.

Echocardiographic assessment

All patients had full echocardiographic examinations at baseline and at study conclusion using a Hewlett Packard Sonos 1500 ultrasonograph (Hewlett-Packard, USA) using standard 2.5 MHz and 3.5 MHz probes. Detailed echocardiographic methods have previously been published (3). The present study focused on measuring LAVs and LA dimensions at baseline and at one year. All echocardiograms were performed and interpreted by two experienced, independent echocardiographers who were blinded to patients, treatment type and timing of the echocardiographic study. M-mode measurements were taken in the left PLAX view by two-dimensionally directed M-mode using American Society of Echocardiography methods (4). LAVs were obtained by carefully tracing LA margins in the apical four chamber and apical two chamber views in atrial systole and diastole. Maximum (atrial diastole) and minimum (atrial systole) LAVs were measured just before mitral valve opening and where the LA appeared the smallest in frame-by-frame analysis, respectively. The plane of the mitral annulus delimited the inferior aspect of the LA, while care was taken to avoid entry of the pulmonary veins when tracing the superior-most margins of the LA. Volumes were derived from these views using the biplane Simpson's method averaging the two-chamber and four-chamber measures. LV mass was calculated using the method published by Devereux and Reichek (5). Measurements were repeated on three consecutive beats and then averaged.

Titration of medical therapy

Patients were blindly and randomly assigned to lisinopril or placebo, administered at an initial daily dose of 5 mg for two weeks. After

day 14, the dose was doubled every two weeks until the maximal dose of 20 mg/day was achieved, the resting (sitting) systolic BP was reduced by 20% from baseline or to a level of 90 mmHg, or symptoms of postural hypotension occurred.

Statistical analysis

The primary end point of the study was the change in LAV and LA dimension over a duration of one year. Continuous variables were reported as mean ± standard deviation. The parametric Student's *t* test was used to compare all normally distributed continuous variables. Categorical variables were compared between groups using the χ^2 test. Statistical significance was defined as $P < 0.05$. The Pearson's correlation coefficient was used to assess the relationship between change in LAV to change in BP and mitral regurgitant fraction. The analysis was based on the intention to treat principle.

RESULTS

Twenty-three patients (16 male and seven female patients, aged 53.2 ± 2.4 years) were randomly assigned to two well-matched groups to receive either lisinopril (12 patients) or placebo (11 patients) for one year. As previously described, there were no significant differences in EF or mitral RF between groups at baseline. Moreover, there were no significant differences at baseline between groups with respect to LA maximum and minimum volumes or LA size measured in PLAX. The average dose of lisinopril was 17 mg/day.

Change in LVEF and RF

Patients treated with lisinopril had a significant decrease in their mitral RF compared with placebo at one year ($-6.4\% \pm 3.5\%$ versus $+3.7\% \pm 3.2\%$, respectively; $P < 0.05$). There was, however, no difference between the lisinopril and placebo groups in overall LVEF ($-1.1 \pm 2.1\%$ versus $-0.4 \pm 1.8\%$, respectively), MR jet to LA area ratio ($-15.7\% \pm 3.7\%$ versus $-10.9\% \pm 2.4\%$, respectively), LV end diastolic dimension ($-0.6\% \pm 1.8\%$ versus $0.2\% \pm 0.5\%$, respectively) or LV end systolic dimension ($-0.7\% \pm 1.4\%$ versus $-0.2\% \pm 0.3\%$, respectively) at one year (P value was not significant for all comparisons).

Change in LAVs and LA dimension

LAVs ranged from 45.8 mL to 161.8 mL in the study population. LA dimensions and maximum and minimum LAVs at baseline and one year are displayed in Table 1. There was no significant difference in maximum LAV at baseline (88.3 ± 33 mL for the lisinopril group versus 88.1 ± 33 mL for the placebo group; $P = \text{not significant}$). At one year, the maximum LAV in the lisinopril group decreased significantly to 75.3 ± 23 mL ($P < 0.01$ versus baseline), while there was no change in the placebo group (91.1 ± 30 mL; $P = \text{not significant}$ versus baseline). Lisinopril therapy was associated with a significant reduction in maximum and minimum LAVs compared with placebo ($-12.7\% \pm 11.4\%$ and $+5.0\% \pm 17.6\%$ for maximum LAV and placebo, respectively [$P < 0.001$]; $-17.0\% \pm 18\%$ versus $-4.4\% \pm 28.7\%$ for minimum LAV and placebo, respectively [$P < 0.001$]) (Figure 1). This decrease in LA size in the lisinopril group at one year compared with baseline was not apparent when LA size was measured by M-mode techniques in the PLAX view (44.5 mm at baseline versus 44.3 mm at one year; $P = \text{not significant}$). Moreover, in contrast with the difference in LAVs between treatment groups, there was no significant

Figure 1) Per cent change (from baseline to one year) in maximum and minimum left atrial (LA) volumes as well as LA dimensions measured using standard M-mode measurements from the parasternal long axis. There was a significant reduction in both maximum and minimum LA volumes in the lisinopril group compared with placebo after one year ($P<0.01$ for both). No difference was found with M-mode-derived LA dimensions

difference in LA dimension between lisinopril and placebo groups at one year when measured by M-mode in the PLAX view (44.3 mm and 46.7 mm, respectively; P =not significant).

Correlation of change in LAV to change in MR fraction

There was no significant correlation between change in maximum or minimum LAV and change in mitral RF in lisinopril-treated patients ($R=0.02$ and $R=0.01$ for maximum and minimum LAV, respectively), while there was a weak correlation in the placebo group ($R=0.44$ and $R=0.62$ for maximum and minimum LAV, respectively).

Effect of systolic BP on change in LAV

At baseline, there was no significant difference in systolic BP between the two groups (124 ± 13 mmHg for the placebo group versus 129 ± 16 mmHg for the lisinopril group; P =not significant). After one year of therapy, however, patients in the lisinopril group experienced a significant decline in systolic BP to 109 ± 10 mmHg ($P<0.01$ versus baseline), while patients in the placebo group did not experience significant change (systolic BP 117 ± 16 mmHg; $P=0.30$ versus baseline). There was no significant correlation between change in systolic BP and change in maximum or minimum LAVs (R values ranging from 0.17 to 0.29 for the lisinopril and placebo groups).

Relationship between LV mass and LAV

At baseline, there was no significant difference in LV mass between the lisinopril and placebo groups (91 ± 8 g/m² versus 93 ± 5 g/m², respectively). At one year, the LV mass decreased by $12\pm 6\%$ in the lisinopril group and increased by $2\pm 5\%$ in the placebo group (P =not significant for comparison between groups). There was a statistically significant and moderate correlation between the change in maximum LAV (but not minimum LAV) with the change in LV mass at 52 weeks ($R=0.43$, $P=0.037$).

Variability of response to lisinopril

There was significant variability in the magnitude of change in LAVs in both the lisinopril and placebo groups (Figure 2). The

Figure 2) Plot of maximal left atrium (LA) volume at baseline and 52 weeks for all subjects in the study

change in LAV in the lisinopril group in minimum LAV ranged from a 7% increase to a 60% decline, while the change in maximum LAV ranged from a 1% increase to a 31% reduction in LAV from baseline to one year. In the placebo group, the change in LAV ranged from +32% to -23% for maximum LAV and from +40% to -34% for minimum LAV. In spite of this variability, six of 11 patients in the placebo group experienced an increase in maximum LAV, compared with only two of 12 patients in the lisinopril group ($P<0.05$). Similar findings were seen in minimum LAV.

Observer variability

Inter- and intraobserver variability was measured for maximum LAV in 11 patients. The interobserver variability was $4\%\pm 12\%$ and the intraobserver variability was $3\%\pm 4\%$.

DISCUSSION

We have previously shown that lisinopril therapy reduces the mitral RF, but not LA size, in the setting of chronic, moderate to severe MR (3). The present study demonstrates that in the setting of moderate to severe MR, lisinopril therapy reduces maximum and minimum LAV measured by biplane Simpson's method, but not LA dimension when measured by M-mode. Therefore, a volumetric approach to the measurement of the LA appears to be superior to standard M-mode techniques.

It has been observed that the LA often expands in three dimensions and eventually assumes a more spherical shape (6). Because standard techniques for assessing LA size involves a two-dimensionally directed M-mode measurement of the LA in the PLAX view, a significant change in LA size may be missed for two reasons if one only uses this standard technique. First, if one considers the LA to roughly approximate a sphere, then small, seemingly insignificant changes in radius can correspond to important changes in volume because the volume of a sphere is proportional to the cube of the radius. For example, a change in LA dimension from 22 mm to 23 mm would result in its volume increasing from 44.6 mL to 50.9 mL – a 12% increase.

Second, the LA may dilate in an asymmetric fashion, with its inferosuperior dimension becoming elongated (1). This plane is not assessed in the standard PLAX orientation, but is

optimally measured from the apex. Measurement of the LA using the biplane Simpson's technique may therefore afford a more exact measurement of LA size because this method takes into account the natural ellipsoid shape of the LA and calculates expansion in three dimensions. This method, as well as the biplane method of disks and three-dimensional echocardiographic methods, has been validated with magnetic resonance imaging, with good correlation but with systematic underestimation of approximately 20% (7). Lester et al (8) noted that the calculation of LAVs using M-mode techniques became increasingly inaccurate with increasing LA size when compared with volumetric assessments using two-dimensional measurements. In contrast, the volumetric assessment of LA using a biplane method of disks showed good agreement with the two-dimensional volumetric assessment of the LA ($R=0.97$).

Clinical implications

There are important potential clinical implications of these data as they pertain to the potential treatment of MR. It is known that increased LA size occurs commonly when LA pressure or volume are elevated, such as with LV dysfunction, LV hypertrophy or MR (9). Treatment of these underlying hemodynamic lesions may therefore blunt the resultant increase in wall stresses, which lead to increased atrial size.

Substantial evidence suggests that increased LA size is associated with atrial fibrillation (AF) (10,11), although it is unclear whether this enlargement is a cause or a consequence of the dysrhythmia itself, or possibly a combination of the two (11,12). Increased LA size has been implicated as an independent risk for stroke in the presence of AF, and successful cardioversion into and maintenance of sinus rhythm is made more difficult in the presence of increased atrial size (13). Therefore, our finding that lisinopril reduced LAVs in the setting of chronic MR may have therapeutic implications beyond merely reducing RF and LAVs. Reductions in LAV could result in a reduction in LA wall stress (14), thereby reducing the atrial electrical remodelling that prefaces AF (15). Indeed, Tsang et al (16) have shown that LAVs provided incremental predictive power for AF over and above that which was offered by measurement of LA dimension, particularly when LA size was in the midrange (4.4 cm to 5.4 cm). Finally, in the clinical arena, Vermees et al (17) and L'Allier et al (18) have recently demonstrated a lower incidence in new-onset AF in hypertensive patients, as well as in patients with congestive heart failure, although they did not have access to echocardiographic data on LA size or volume.

It is not surprising that there was significant variability in change in LAV within the groups. It is interesting to note, however, the lack of correlation between change in LAV and change in MR fraction in the lisinopril-treated group, whereas a weak correlation was noted in the placebo group. While the numbers are small in both groups, this raises the possibility that lisinopril is acting on the LA to reduce its volume in a way other than by just reducing the volume of regurgitation imparted on it. This may be supported by the significant, moderate correlation between change in LAV and change in LV mass in the entire study population. Perindopril, another ACE inhibitor, has been shown to reduce LAV in a group of hypertensive patients (19). While the systolic BP did decrease significantly in the lisinopril arm, there was no significant correlation between this decline and the LAV. In a rapid pacing model of congestive heart failure in dogs (20), treatment with

enalapril resulted in an attenuation of LA dilation. This attenuation was highly correlated with a decrease in LA fibrosis (20).

Study limitations

The present study had several limitations. We did not have access to true three-dimensional assessment using multiple planes due to the retrospective nature of the data analysis. Therefore, it is possible that irregular enlargement of the LA was missed by volumetric assessment of LA size. However, the Simpson's method of volumetric assessment in three dimensions would still be more accurate in determining the size of even an irregular sphere than would traditional orthogonal measurements in two dimensions.

Furthermore, our study was not powered to address the effect of the reduction of LAV on the incidence of clinical events, such as AF, due to its small sample size. Only one patient (in the lisinopril group) developed AF in the one year of follow-up. Given the results of the present study, further work on the effects of reduction in LA size and pressure on the incidence of AF appears warranted.

CONCLUSIONS

Long-term use of lisinopril reduces LAVs in the setting of chronic MR. This difference in LA size was not appreciated when the LA was measured using standard M-mode techniques. A volumetric approach to the assessment of LA size appears to be superior to standard measurement techniques using two-dimensionally guided M-mode echocardiography.

ACKNOWLEDGEMENTS: The authors thank Drs George Honos and Anne Walling, as well as Marie-Josée Blais, Carole Daoust and Desneiges Beauvais for their important contributions to the original study.

FUNDING: This study was supported by a grant from Merck Frosst Canada Inc, and from the Bank of Montreal Research Center for the Study of Heart Disease in Women at the Sir Mortimer B Davis Jewish General Hospital, McGill University, Montreal, Quebec.

REFERENCES

1. Left ventricular inflow tract II: The left atrium, pulmonary veins, and coronary sinus. In: Weyman AE, ed. *Principles and Practice of Echocardiography*, 2nd edn. Philadelphia: Lippincott Williams & Wilkins, 1994:471-97.
2. Dujardin KS, Enriquez-Sarano M, Bailey KR, Seward JB, Tajik AJ. Effect of losartan on degree of mitral regurgitation quantified by echocardiography. *Am J Cardiol* 2001;87:570-6.
3. Marcotte F, Honos GN, Walling AD, et al. Effect of angiotensin-converting enzyme inhibitor therapy in mitral regurgitation with normal left ventricular function. *Can J Cardiol* 1997;13:479-85.
4. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: Results of a survey of echocardiographic measurements. *Circulation* 1978;58:1072-83.
5. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. *Circulation* 1977;55:613-8.
6. Loperfido F, Pennestri F, Digaetano A, et al. Assessment of left atrial dimensions by cross sectional echocardiography in patients with mitral valve disease. *Br Heart J* 1983;50:570-8.
7. Rodevan O, Björnerheim R, Ljosland M, Maehle J, Smith HJ, Ihlen H. Left atrial volumes assessed by three- and two-dimensional echocardiography compared to MRI estimates. *Int J Card Imaging* 1999;15:397-410.

8. Lester SJ, Ryan EW, Schiller NB, Foster E. Best method in clinical practice and in research studies to determine left atrial size. *Am J Cardiol* 1999;84:829-32.
9. Braunwald E. Valvular heart disease. In: Braunwald E, Zipes DP, Libby P, eds. *Heart Disease: A Textbook of Cardiovascular Medicine*. Philadelphia: WB Saunders Company, 2001:1643-714.
10. Henry WL, Morganroth J, Pearlman AS, et al. Relation between echocardiographically determined left atrial size and atrial fibrillation. *Circulation* 1976;53:273-9.
11. Andersen JS, Egeblad H, Abildgaard U, Aldershvile J, Godtfredsen J. Atrial fibrillation and left atrial enlargement: Cause or effect? *J Intern Med* 1991;229:253-6.
12. Thamilarasan M, Klein AL. Factors relating to left atrial enlargement in atrial fibrillation: "Chicken or the egg" hypothesis. *Am Heart J* 1999;137:381-3.
13. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA* 1994;271:840-4.
14. Sideris DA, Toumanidis ST, Tselepatiotis E, et al. Atrial pressure and experimental atrial fibrillation. *Pacing Clin Electrophysiol* 1995;18:1679-85.
15. Ravelli F, Allesie M. Effects of atrial dilatation on refractory period and vulnerability to atrial fibrillation in the isolated Langendorff-perfused rabbit heart. *Circulation* 1997;96:1686-95.
16. Tsang TS, Barnes ME, Bailey KR, et al. Left atrial volume: Important risk marker of incident atrial fibrillation in 1655 older men and women. *Mayo Clin Proc* 2001;76:467-75.
17. Vermees E, Tardif JC, Bourassa MG, et al. Enalapril decreases the incidence of atrial fibrillation in patients with left ventricular dysfunction: Insight from the Studies Of Left Ventricular Dysfunction (SOLVD) trials. *Circulation* 2003;107:2926-31.
18. L'Allier PL, Ducharme A, Keller PF, Yu H, Guertin MC, Tardif JC. Angiotensin-converting enzyme inhibition in hypertensive patients is associated with a reduction in the occurrence of atrial fibrillation. *J Am Coll Cardiol* 2004;44:159-64.
19. Yalcin F, Aksoy FG, Muderrisoglu H, Sabah I, Garcia MJ, Thomas JD. Treatment of hypertension with perindopril reduces plasma atrial natriuretic peptide levels, left ventricular mass, and improves echocardiographic parameters of diastolic function. *Clin Cardiol* 2000;23:437-41.
20. Shi Y, Li D, Tardif JC, Nattel S. Enalapril effects on atrial remodeling and atrial fibrillation in experimental congestive heart failure. *Cardiovasc Res* 2002;54:456-61.