The Association of Left Atrial Volume with Exercise Capacity in Patients with Chronic Severe Mitral Regurgitation

Mordehay Vaturi MD, Tanya Hadar MD, Idit Yedidya MD, Yaron Shapira MD, Daniel Monakier MD, Daniel E. Weisenberg MD and Alex Sagie MD

Echocardiography Unit and Valvular Clinic, Department of Cardiology, Rabin Medical Center (Beilinson Campus), Petah Tikva, and Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

ABSTRACT: **Background:** Left atrial volume and exercise capacity are strong predictors of cardiovascular risk. Decreased exercise capacity is expected when LAV is increased due to its association with abnormal left ventricular filling pressure. However, LAV enlargement is expected in chronic mitral regurgitation as well.

Objectives: To examine the link between LAV and exercise capacity in chronic MR and to determine whether larger LAV has indeed better exercise capacity in patients with chronic severe degenerative MR and good LV systolic function.

Methods: The study included asymptomatic patients with severe chronic degenerative MR and normal LV systolic function that underwent stress echocardiography. LAV was measured at rest using the biplane Simpson's method and indexed to body surface area. The cutoff of good exercise capacity was determined at 7 METS.

Results: The patient group comprised 52 consecutive patients (age 60 ± 14 years, 36 males). Two subgroups (19 vs. 33 patients), age- and gender-matched, were formed according to LAVi cutoff of 42 ml/m^2. Those with higher LAVi had lower exercise capacity ($P = 0.004$) albeit similar MR grade, baseline blood pressure, LV function and size. Receiver-operator curve analysis revealed indexed LAV value of ≤ 42 as 51% sensitive and 88% specific for predicting exercise capacity › 7 METS (AUC = 0.7, $P = 0.03$). In multivariate analysis, age, gender and LAVi were identified as independent predictors of exercise capacity.

Conclusions: In asymptomatic patients with severe chronic degenerative MR and normal LV systolic function, mild enlargement of the left atrium (≤ 42 ml/m^2) is associated with good exercise capacity.

IMAJ 2010; 12: 150–153

KEY WORDS: left atrium, left atrial volume, degenerative mitral regurgitation, exercise capacity

LAV = left atrial volume
MR = mitral regurgitation
LV = left ventricular
LAVi = LAV indexed to body surface area
AUC = area under the curve

Enlarged left atrial volume is an accepted indicator of cardiovascular risk burden [1]. Studies have determined the association between enlarged LAV and increased risk for a first cardiovascular event in an elderly cohort [2], and with all-cause mortality after acute myocardial infarction [3]. The association between low exercise capacity and poor prognosis is also well established in normal subjects [4] and in various cardiac [4-6] and pulmonary [7] diseases. However, in the absence of systolic left ventricular dysfunction, coronary artery disease or significant valvular disease, abnormal LV filling may play a key role in limiting exercise capacity [8,9]. Indeed increased LAV has been associated with abnormal LV filling pressures [1,10-12].

Although enlargement of the left atrium is expected in patients with severe chronic mitral regurgitation, the relation of LA size and exercise capacity in these patients remains unknown. Intuitively, a larger LA is expected in patients with good exercise capacity due to better capacity for large regurgitation volume. Thus, the aim of this study was to examine this assumption and to determine whether larger LAV has indeed better exercise capacity in patients with chronic severe degenerative MR and good LV systolic function.

PATIENTS AND METHODS

The echocardiography database of Rabin Medical Center was reviewed for patients (age ≥ 18 years) with severe degenerative MR (severity determined by current echocardiography guidelines [13]). The selected patients underwent exercise stress echocardiography between 2004 and 2006 as a routine follow-up. The study group comprised patients in stable condition, asymptomatic, or with non-specific symptoms. Exclusion criteria included evidence of acute coronary ischemia, LV dysfunction (ejection fraction < 50%), valvular disease other than chronic severe mitral regurgitation (i.e., mitral stenosis and/or aortic stenosis/regurgitation), atrial

LA = left atrium

fibrillation, history of heart transplantation, congenital heart disease, and suboptimal echocardiographic study (i.e., inadequate to trace the LA endocardial border in the apical views). Beta-blockers were withheld at least 24 hours prior to the study as per protocol.

The data regarding heart rate, blood pressure and relevant exertion symptoms (chest pain, dyspnea), indication for the study, and medical history were obtained from the medical records. Body surface area was calculated for each patient.

ANALYSIS

All stress echocardiography studies were performed with treadmill exercise using standard symptom-limited protocols. The two-dimensional echo images were obtained at rest and immediately with exercise cessation using the standard views to assess ischemia. The endocardial border of the left atrium was traced at end-systole and end-diastole in the apical four- and two-chamber views. Views with atrial foreshortening were avoided by using visual evaluation and selecting the frames with the greater LA dimensions in each apical view. The LA appendage and the pulmonary venous confluence were excluded from the traced area and a straight line between mitral annular hinge points was drawn. LA volume was determined by the biplane Simpson's method at end-systole (just before opening of the mitral valve) and end-diastole (just before the mitral valve closure). The volumes were indexed by body surface area. The thickness of the interventricular septum, posterior wall, and the basal LV end-diastolic diameter were obtained from a two-dimensional image at the parasternal long axis [14]. Right ventricular systolic pressure was calculated using the modified Bernoulli formula based on the tricuspid regurgitation Doppler signal. RVSP was measured at rest and immediately at the end of the exercise. The threshold between low and good exercise capacity was set at 7 METS [15,16].

STATISTICAL ANALYSIS

The results are presented as mean ± SD for continuous variables. Comparison between groups was done by unpaired *t*-test and Fisher's exact test, as appropriate. The association between exercise capacity and age, gender and indexed LA volume was evaluated by multiple regression analysis. Receiver-operator characteristic curve was generated to estimate the predictability of exercise capacity by the pretest indexed LAV. Significance was defined as $P < 0.05$ (two-tailed) for all analyses.

The LA volumes were measured separately by two cardiologists (both were blinded to each other's measurements). The intra- and interobserver variability was calculated using the interclass correlation coefficient. A value ≥ 0.9 was indicative of a very good matching between observations.

RVSP = right ventricular systolic pressure

RESULTS

The study group consisted of 52 adults (36 males, mean age 59 ± 14 years, range 31–83). The indication for the stress studies was functional class and dynamic assessment of the change in pulmonary pressure from rest to peak exercise. In 23 patients (44.2%) the target age-adjusted maximal heart rate was achieved, whereas in the other patients the exercise was terminated because of fatigue and dyspnea. The average exercise capacity for the entire group was 10.1 ± 3.3 METS. There was insignificant inter-gender differences in age, LV dimension, RVSP (at rest and at peak exercise), exercise capacity and indexed LAV. However, most of the female patients ceased exercise prematurely because of fatigue (81% vs. 44% respectively, $P = 0.01$).

The receiver-operator curve analysis revealed an indexed LAV value of ≤ 42 as 51% sensitive and 88% specific for predicting exercise capacity > 7 METS (AUC = 0.7, $P = 0.03$) [Figure 1]. Thus, two subgroups of patients were formed based on indexed LAV: group A (n=19, < 42 ml/m²) and group B (n=33, ≥ 42 ml/m²). The two groups were significantly different in their exercise capacity: 11.8 ± 2.4 vs. 9.1 ± 3.4 METS respectively, $P = 0.004$ [Table 1]. All the patients in group A had exercise capacity > 7 METS, whereas the patients in group B were equally distributed below and above this value [Figure 2]. Both groups had severe MR (same mean vena contracta) and similar blood pressure at the time of MR estimation [Table 1]. The two groups had similar RVSP at rest and at peak exercise and similar grades of tricuspid regurgitation. However, RVSP (rest and peak) was significantly lower among the patients with good exercise capacity (> 7 METS), namely, rest: 28 ± 10.2 vs. 37.3 ± 11.8 mmHg

AUC = under the curve

Figure 1. Receiver operator characteristic curve for the prediction of exercise capacity by indexed LAV (area under the curve 0.67, $P = 0.03$)

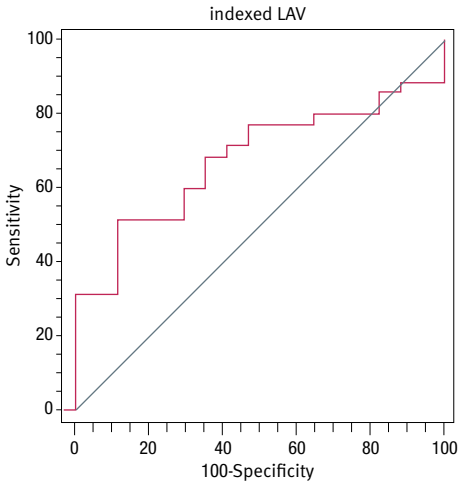

Figure 2. Patient distribution according to indexed LAV (42 ml/m2) and exercise capacity (7 METS)

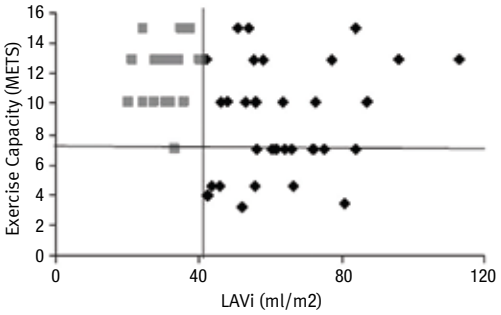

Table 1. Patient characteristics

	Group A (n=19)	Group B (n=33)	*P* value
Exercise capacity (METS)	11.8 ± 2.4	9.1 ± 3.2	0.004
LVEDd (mm)	4.7 ± 0.5	5.0 ± 0.7	NS
LVESd (mm)	2.9 ± 0.4	3.1 ± 0.5	NS
MR jet vena contracta (cm)	0.7 ± 0.1	0.7 ± 0.1	NS
SBP (mmHg)*	137 ± 18	133 ± 19	NS
DBP (mmHg)*	80 ± 6	78 ± 8	NS
RVSP rest (mmHg)	28.8 ± 12.9	32.3 ± 10.6	NS
RVSP peak (mmHg)	45.2 ± 9.5	50.1 ± 13.3	NS
Tricuspid regurgitation grade			
None	13	6	NS
Mild	5	22	
Moderate	1	5	
Severe	0	0	

LVEDd = LV end-diastolic dimension, LVESd = LV end-systolic dimension
* Systolic (SBP) and diastolic (DBP) pressures at the time of MR grade estimation

respectively, $P = 0.01$; peak: 37.9 ± 16.3 vs. 52.4 ± 19.9 mmHg respectively, $P = 0.02$.

In a subgroup of 35 patients, data regarding previous echocardiographic studies (at least two consecutive studies) were available. In this subgroup, the average duration of severe MR was 41.5 ± 28.2 months (range 1–108 months). There were insignificant differences in the duration of severe MR between these patients when divided by the cutoff of exercise capacity > 7 METS (45 ± 31.6 vs. 34 ± 17.6 months, respectively, $P = 0.2$), or when divided by the cutoff of LAVi (≥ 42 ml/ml2): 45.1 ± 32.3 vs. 34.6 ± 16.9 months, $P = 0.2$).

In multiple regression analysis using indexed LAV as a continuous value, the main determinants of exercise capacity in the study group were increased age (beta -0.59, $P < 0.001$), female gender (beta -0.26, $P < 0.05$), and increased indexed LAV (beta -0.28, $P < 0.01$).

The intra- and interobserver variability for the measurement of LA volume was very good (ICC 0.99 and 0.93, respectively).

DISCUSSION

This study showed that in patients with chronic severe degenerative MR and normal LV systolic function, exercise capacity is better when LA enlargement is still relatively mild (LAVi < 42 ml/m2). LA enlargement, though sensitive to the effect of many factors, was identified in this study as an independent predictor of the patients' exercise capacity. However, the association with exercise capacity was inconclusive in the patients who had the relatively larger atrium (LAVi ≥ 42 ml/ml2). The possible explanation for this finding might be that the relatively smaller LA identifies a group of patients with better hemodynamics to begin with. Since the intersubject variability in LA size could not be explained exclusively by differences in MR severity or duration of the severe MR, it might be assumed that with further LA enlargement the hemodynamics become less favorable. This would be reflected by a decrease in exercise capacity and elevation of RVSP (secondary to elevation in LA pressure).

Decreased functional capacity in chronic MR is an important landmark in the management and prognosis of the disease [17]. Increased LA diameter had been identified as an independent predictor of worse outcome in a cohort of patients with a flail mitral valve (who were not homogeneous in functional class and heart rhythm) [18]. The current study highlights the finding that although enlarged [19], the magnitude of LA enlargement can be a useful parameter in the stratification of asymptomatic patients with severe chronic MR and normal LV systolic function.

STUDY LIMITATIONS

The study is retrospective with a referral-based cohort. Thus, correlation to LV filling parameters or matching patients by their pre-study physical fitness was not possible. A drawback in comparing LA size between subjects with severe MR is the potential impact of the duration of the mitral pathology. To resolve this issue we provided data showing similar duration of severe MR between the two study subgroups. A delay between onset of severe MR and its diagnosis is possible in asymptomatic patients. Thus, we provided data only for the patients who underwent at least two consecutive echocardiographic studies in our laboratory (67% of the entire cohort).

LA volume is determined by LV function and loading condition. In this study, LA loading was not monitored invasively and could not be precisely matched between the groups. Nevertheless, the two groups were matched by their systolic LV function (normal by default) and in LV dimensions. The

ICC = interclass correlation coefficient

MR grade was similar and under similar blood pressure in both groups at the time of LAV assessment. Apical imaging of the LA can be sensitive to suboptimal lateral resolution of the ultrasound beam; however, this limitation is shared by the entire cohort, and the biplane method to calculate the LAV is an established and validated echocardiography method [20,21].

CONCLUSIONS

In asymptomatic patients with chronic severe degenerative MR, normal LV systolic function and indexed LAV < 42 ml/m^2, one might expect good exercise capacity. However, the entire spectrum of LA adaptation to chronic MR and its impact on prognosis need further investigation.

Correspondence:
Dr. M. Vaturi
Echocardiography Unit and Valvular Clinic, Dept. of Cardiology, Rabin Medical Center (Beilinson Campus), Petah Tikva 49100, Israel
Phone: (972-3) 937-7056, **Fax:** (972-3) 937-7055
email: mvaturi@clalit.org.il

References

1. Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. *Am J Cardiol* 2002; 90: 1284-9.
2. Tsang TS, Barnes ME, Gersh BJ, et al. Prediction of risk for first age-related cardiovascular events in an elderly population: the incremental value of echocardiography. *J Am Coll Cardiol* 2003; 42: 1199-205.
3. Moller JE, Hillis GS, Oh JK, et al. Left atrial volume: a powerful predictor of survival after acute myocardial infarction. *Circulation* 2003; 107: 2207-12.
4. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002; 346: 793-801.
5. Kavanagh T, Mertens DJ, Hamm LF, et al. Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation. *Circulation* 2002; 106: 666-71.
6. Almendral JM, Garcia-Andoain JM, Sanchez-Cascos A, de Rabago P. Treadmill stress testing in the evaluation of patients with valvular heart disease. Possible role in the assessment of functional capacity and severity of the lesion. *Cardiology* 1982; 69: 42-51.
7. Bowen JB, Votto JJ, Thrall RS, et al. Functional status and survival following pulmonary rehabilitation. *Chest* 2000; 118: 697-703.
8. Hundley WG, Kitzman DW, Morgan TM, et al. Cardiac cycle-dependent changes in aortic area and distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance. *J Am Coll Cardiol* 2001; 38: 796-802.
9. Little WC, Kitzman DW, Cheng CP. Diastolic dysfunction as a cause of exercise intolerance. *Heart Fail Rev* 2000; 5: 301-6.
10. Appleton CP, Galloway JM, Gonzalez MS, Gaballa M, Basnight MA. Estimation of left ventricular filling pressures using two-dimensional and Doppler echocardiography in adult patients with cardiac disease. Additional value of analyzing left atrial size, left atrial ejection fraction and the difference in duration of pulmonary venous and mitral flow velocity at atrial contraction. *J Am Coll Cardiol* 1993; 22: 1972-82.
11. Simek CL, Feldman MD, Haber HL, Wu CC, Jayaweera AR, Kaul S. Relationship between left ventricular wall thickness and left atrial size: comparison with other measures of diastolic function. *J Am Soc Echocardiogr* 1995; 8: 37-47.
12. Briguori C, Betocchi S, Losi MA, et al. Noninvasive evaluation of left ventricular diastolic function in hypertrophic cardiomyopathy. *Am J Cardiol* 1998; 81: 180-7.
13. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003; 16: 777-802.
14. Weyman AE. Principles and Practice of Echocardiography. Philadelphia: Lea & Febiger, 1993: 602.
15. Snader CE, Marwick TH, Pashkow FJ, Harvey SA, Thomas JD, Lauer MS. Importance of estimated functional capacity as a predictor of all-cause mortality among patients referred for exercise thallium single-photon emission computed tomography: report of 3,400 patients from a single center. *J Am Coll Cardiol* 1997; 30: 641-8.
16. Pilote L, Silberberg J, Lisbona R, Sniderman A. Prognosis in patients with low left ventricular ejection fraction after myocardial infarction. Importance of exercise capacity. *Circulation* 1989; 80: 1636-41.
17. Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 Guidelines for the Management of Patients with Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients with Valvular Heart Disease): Developed in Collaboration with the Society of Cardiovascular Anesthesiologists: Endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation* 2006; 114: e84-231.
18. Ling LH, Enriquez-Sarano M, Seward JB, et al. Clinical outcome of mitral regurgitation due to flail leaflet. *N Engl J Med* 1996; 335: 1417-23.
19. Oh JK, Seward JB, Tajik AJ. The Echo Manual. Philadelphia: Lippincott Williams & Wilkins, 2006: 431.
20. Schiller NB, Foster E. Analysis of left ventricular systolic function. *Heart* 1996; 75: 17-26.
21. 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.