Left Atrial Volume Index (LAVI) is a Predictor of Exercise Functional Capacity in Patients with Rheumatic Mitral Stenosis

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Background --- Left Atrial Volume Index (LAVI) has recently found its significance in several settings of left ventricular diastolic as well systolic dysfunctions. It predicts poor exercise tolerance in patients with dilated and hypertrophic cardiomyopathy and in atrial fibrillation. It has become a powerful predictor of mortality in patients after myocardial infarction. Surprisingly, all studies excluded patients with rheumatic heart disease. It has been established that due to chronic exposure of patients with Rheumatic Mitral Stenosis (MS) to high left atrial pressures, LA dilatation ensues with consequent elevation in left atrial volume index. Such pressure will likewise be reflected backward to the pulmonary circulation causing an increase in pulmonary artery pressure (PAP). We hypothesized that LAVI could be an indirect surrogate of PAP which is an objective measure of functional capacity. Therefore, correlating LAVI with proven measures of functional capacity including Systolic PAP and METS achieved on peak exercise could lead us to another value of LAVI in this subset of patients. Thus, we sought to investigate whether LAVI predicts functional capacity in patients with rheumatic mitral stenosis.

Methods --- We employed a prospective, cross-sectional study design. Seventeen (17) of forty-five (45) prospective patients with Rheumatic mitral stenosis seen at the OPD of the Philippine Heart Center from August to December 2007 were studied. Patients with mild to moderate MS with NYHA FC II, asymptomatic severe MS, age < 50 years, adequate systolic function & resting SPAP < 50mmHg were included. Baseline echocardiographic studies were obtained to measure the mitral valve area and gradient, LAVI, LA ejection fraction and SPAP by peak Tricuspid Regurgitation (TR) gradient. Treadmill Exercise Tests using the NEPTET protocol were done followed by Doppler echocardiographic studies at peak exercise. The relationship between continuous variables was determined by the Spearman-Rank coefficient, ROC curve and student's t-test. A p-value <0.05 was considered significant.

Results --- The mean resting LAVI of patients was 58 + 20 cc/m2. There was good correlation between resting LAVI and functional capacity measured by both METS and peak SPAP achieved (R=0.67 and 0.61 respectively). Based on METS achieved, lower LAVI values were found in Class I (45 + 10 cc/m2) than in Class II (59 + 10) and Class III (82 + 33) with a p-value of 0.02. Based on SPAP achieved on peak exercise, patients with good functional capacity had a LAVI of 44 + 12 cc/m2 compared to patients with poorer functional capacity, 67 + 21 (p =0.02). LAVI < 45 cc/m2 best predicted a good functional capacity with sensitivity, specificity, PPV and NPV of 90%, 71%, 82% and 83% respectively.

Conclusion --- Left atrial volume index is both a good predictor and an objective measure of exercise functional capacity among patients with Rheumatic mitral stenosis and can be used in lieu of more expensive tests when cost-effectiveness matters to patient management. *Phil Heart Center J 2008; 14(1):14-19.*

Key Words: Left atrial volume index ■ Mitral Stenosis ■ Functional capacity ■ Echocardiography ■ Exercise Stress Test

Indices of Left Atrial function such as decreased LA Ejection Fraction and increased atrial volume were significantly correlated with poor exercise tolerance in patients with left ventricular systolic dysfunction, specifically in dilated cardiomyopathy.[1]

In recent years, LAVI (cc/m2) is increasingly recognized as a relatively load-independent marker of LV filling pressure and has been a surrogate marker of diastolic function in many studies. First, it was shown that in patients after acute myocardial infarction, LAVI >32ml/m2 was a powerful predictor of mortality after adjustment for clinical factors, and both markers of systolic & diastolic dysfunction.[2]

Likewise, LAVI >26ml/m2 was an independent predictor of LV diastolic dysfunction as predicted by elevated serum BNP.3 In patients with hypertrophic

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cardiomyopathy, LAVI>36ml/m2 was noted to be an independent predictor of decreased exercise capacity.[4] Finally, in patients with non-valvular atrial fibrillation, LAVI >55 ml/m2 was associated with a decreased exercise capacity <7 METS.[5] Interestingly, all studies on LAVI, however excluded patients with rheumatic heart disease.

The fundamental hemodynamic feature of MS is the elevation of Left Atrial Pressure (LAP) which raises pulmonary venous pressure causing exertional dyspnea. Backward transmission of this pressure likewise causes elevation of Systolic Pulmonary Arterial Pressure (SPAP).[6] Left atrial enlargement is one of the markers of the magnitude of LA pressure elevation.7 Although LA volume probably reflects long-term exposure of the LA to increased LA pressures, no study has yet shown that Left Atrial Volume Index (LAVI) is associated with the level of LA pressure and SPAP.

Functional capacity (FC) constitutes one of the major indications for intervention among patients with Rheumatic Mitral Stenosis (MS).[8, 9] However, variation in individual perception of activity limitation has led to inappropriate NYHA functional classification and subsequent treatment recommendation.

Functional capacity can be objectively measured using the level of METS achieved on TET and level of SPAP determined on Doppler echocardiography at peak exercise. No study has yet shown a correlation between functional capacity assessed by NYHA & treadmill exercise test in patients with rheumatic mitral stenosis. Recent guidelines for intervention in asymptomatic/FC I or FC II patients require further evaluation via Exercise Echocardiography.[8] It has been established that the most important determinant of exercise tolerance or functional capacity in MS patients is the level of SPAP obtained during exercise.[10] SPAP >60mmHg achieved at peak exercise warrants Percutaneous Mitral Balloon Valvotomy (PMBV) in asymptomatic moderate to severe MS (Class I) & FC II mild MS (Class IIb).[8] Mean Valve Gradient (MVG) likewise is the only independent factor for increased SPAP with exercise.[10, 11] MVG > 15mmHg at peak exercise is also an indication for PMBV for such patients.[8]

LAVI is a parameter easily measured on echocardiographic studies. Since LAVI is expectedly increased in patients with rheumatic MS especially in those with elevated LA pressure, we hypothesize that in this subset of patients, an elevated LAVI could reflect an elevated SPAP and poorer exercise FC measured in METS. This study aims to investigate whether resting LAVI correlates with the level of functional capacity assessed by TET (METS) and Exercise Doppler Echocardiography (SPAP).

If a correlation exists between the level of LAVI and Exercise Functional Capacity of Rheumatic MS patients, the former can be considered among others as an important parameter in the algorithmic approach to patient management. Hence, with the recent guidelines being modified, functional capacity can be assessed by LAVI without the further need of other costly diagnostic tests.

Methods

We employed a prospective, cross-sectional study design wherein we screened consecutive patients with rheumatic mitral stenosis seen at the Outpatient Department and Non-invasive Diagnostic Division of the Philippine Heart Center from August to December 2007. Included were patients with mild to Moderate MS (MVA>=1.0 cm2) in NYHA FC I-II or asymptomatic (NYHA FC I) Severe MS (MVA<1cm2), age <50 years old, normal LVEF and resting Systolic Pulmonary Arterial Pressure (SPAP) <50mmHg. Excluded were the following: patients with moderate to severe MS in NYHA FC III-IV; moderate to severe MS in NYHA FC II with Pulmonary Hypertension (SPAP>50); those with concomitant Significant Regurgitation other than TR; those with significant valvular stenosis other than MS; those who were post-PMBV/Mitral Valve Replacement (MVR); those with LV Systolic Dysfunction (EF<40); presence of the following co-morbidities, such as CAD, COPD, Cardiomyopathy, Anemia, LA thrombus; and contraindications to TET.

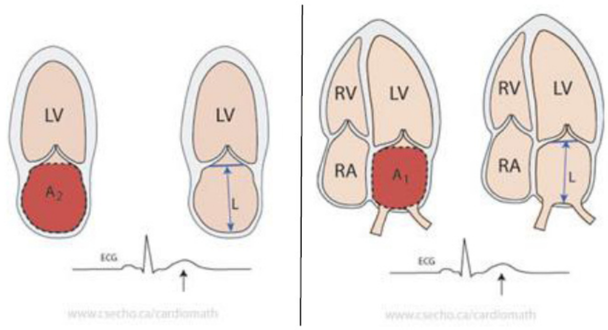
Out of 45 patients initially screened, 17 patients with Rheumatic mitral stenosis were included in the study. Prospective patient's functional capacity was classified based on NYHA criteria. Baseline 2D Echocardiographic studies were done. In the absence of contraindications (fever, hypotension, hemodynamically significant arrhythmias, inability to walk, severe aortic stenosis), these patients underwent TET.

Echocardiographic Data

Baseline Mitral Valve Area (MVA) by Pressure Half Time (PHT) &Planimetry (PLN), Mean Valve Gradient, SPAP via Peak Tricuspid regurgitation (TR) gradient, LA Size, and LV EF were obtained before Treadmill Exercise Test. Left Atrial Volume Index (LAVI was likewise measured as follows: Both height (cm) and weight (kg) of all patients were taken to compute for the Body Surface Area (BSA). LAVI of all patients using the Biplane Area-Length Method were then properly measured during ventricular endsystole. Area1 and Length1 & Area2 and Length2 were measured on both apical 4& 2-chamber views respectively. (Figure 1)

The following formula was used to compute for LAVI:

$$LAVI = \frac{Area1 \times Area2 \times 0.85 / Length\ (shorter\ of\ Length\ 1\ \&\ 2)}{Body\ Surface\ Area}$$



Apical 2C Apical 4C

Figure 1. Measurement of the variables needed in the computation for LAVI.
(A1- area of LA on apical 4-chamber view, A2- Area of LA on apical 2-chamber view, L-length of LA, LV- left ventricle, RV- right ventricle, RA- right atrium) Adapted from www.csecho.ca/cardiomath.

Baseline Functional Capacity of all patients was assigned to patients based on the New York Heart Association (NYHA)

Treadmill Exercise Test Followed By Stress Doppler Echocardiography

A symptom-limited Treadmill Exercise Test using the NIH/NEPTET protocol was done. Immediately after termination of exercise, with the patient at the left lateral decubitus position, the Systolic Pulmonary Arterial Pressure (SPAP) estimated using the Peak TR gradient, the Mean Valve Gradient, MVA by PHT, LAVI and LA Ejection Fractions were again measured within the 1st minute of peak exercise. The mean of 3 beats was taken for patients in sinus rhythm while the mean of 5 beats after the long cycle length was recorded for patients in atrial fibrillation. The Exercise Time *(time the patient will be able to exercise before stopping due to symptoms)* as well as the reason for exercise termination were recorded.

Sample Size

Ideal sample size includes 62 patients with 80% accuracy at $\lambda = 0.05$, total relative error of 20%, desired precision of 10%, with expected prevalence of 80% at 95% Confidence Interval.

Statistical Analysis

Continuous variables were presented as mean +/- SD while nominal data were described as frequency & percent distribution. The relationships between variables were evaluated using Spearman-Rank correlation coefficient, ROC curve & independent t-test. Validity measures were determined and a p-value <0.05 was considered significant.

Results

There were 45 patients initially for screened for inclusion but due to presence of severe pulmonary hypertension (15 patients), depressed ejection fraction (8 patients) and LA thrombus (5 patients), only 17 patients finally qualified for evaluation. Baseline characteristics of the 17 patients were presented in Table 1. There were more females than males with a mean age of 35 + 8.2 years. More patients were in sinus rhythm than in atrial fibrillation. Eleven patients had severe MS while six had moderate MS. The average MVA by PHT & PLN were 0.93 cm2 & 0.89cm2 respectively with a MVG of 10 + 2 mmHg. All patients had adequate systolic function with an average ejection fraction of 65 + 6 mmHg. Left atria of all patients were dilated with a mean size of 4.9 + 0.9 cm. The mean resting LA ejection fraction was 24 % (+10). Based on NYHA classification, most patients belong to Class I than Class II.

Table 2 shows the following parameters noted on Treadmill Exercise Test. The mean of METS achieved was 5.6 + 2.2 while the average exercise time spent on TET was 13 + 7 minutes with shortness of breath as the most common indication for termination. Functional capacity based on METS achieved classified patients into Class I (8), Class II (4), Class III (2) and Class IV (3).

Variables of functional capacity both at rest and peak exercise were summarized in Table 3. There was no statistical difference between the mean LAVI at rest and at peak exercise (57.7 vs.57.8 cc/m2, p=0.99). The other two variables of functional capacity that were significantly higher at peak exercise than at rest were Mean Valve Gradient (18.3 vs. 10 mmHg, p<0.001) and SPAP (56 vs. 37 mmHg, p<0.001).

Table 4 shows that as functional capacity of patients based on METS achieved at peak exercise declined from Class I to Class III, the value of resting LAVI also increased (p = 0 .02). That is, LAVI was significantly lower in Class I (45 +10) compared to Class II (59 +100) and Class III (82 +33). Using the Spearman-Rank Coefficient analysis (Figure 2), there was good correlation between functional capacity based on METS achieved with resting LAVI (R=0.67, p=0.003).

Table 5 shows that patients with LAVI < 44cc/m2 have lower peak SPAP indicating a good functional capacity (Class I) while those with a higher LAVI > 67 cc/m2 have a higher peak SPAP indicating poorer, Class II functional capacity (p<0.02). Figures 3 demonstrate good correlation of resting LAVI with exercise FC determined by peak SPAP with R=0.61 & p-value of

0.02. The best cut-off value of resting LAVI to predict a poor FC (SPAP> 60mmHg) is > 45 cc/m2 with sensitivity, specificity, PPV and NPV of 90%, 71%, 82% and 83% respectively (Table 6). An ROC curve also shows that LAVI > 45cc/m2 best predicts a poor exercise FC (Figure 4).

Table1. Baseline Characteristics of Included Patients

Characteristics	Frequency / Mean (SD) N=17
Age	35 (8.2)
Sex (female)	13
Rhythm	
Atrial Fibrillation	5
Sinus	12
Severity of Mitral Stenosis	
Moderate	6
Severe	11
NYHA Functional Class	
I	10
II	7
Mitral Valve Area	
Pressure Half-time (cm^2)	0.93 (0.31)
Planimetry (cm^2)	0.89 (0.34)
Mean Valve Gradient (mmHg)	10 (4.2)
LV Ejection Fraction (%)	65 (6)
LA Size (cm)	4.9 (0.97)
LAVI (cc/m^2)	57.7 (20.1)
SPAP (mmHg)	37.2 (9.7)

Table 2. Treadmill Exercise Test Parameters of Included

Parameter	Frequency / Mean (SD) N=17
METS achieved	5.6 (2.2)
Total Exercise Time (min)	13 (7)
NYHA Functional Class	
I	8
II	4
III	2
IV	3
Reason for Termination	
Shortness of breath	9
Exhaustion	6
Leg Fatigue	1

Table 3. Variables of Functional Capacity at Rest and at Peak Exercise

Variables	Rest (mean ± SD)	Peak Exercise (mean ± SD)	p-value	Remarks
LAVI (cc/m^2)	58 ± 21	58 ± 23	0.99	Not significant
SPAP (mmHg)	10 ± 4	18 ± 9	<0.001	Significant
MVG (mmHg)	37 ± 10	56 ± 21	<0.001	Significant

Table 4. Comparison of Resting LAVI with Peak Exercise Functional Capacity Based on Amount of METS Achieved

Functional Capacity Class	Resting LAVI Mean	SD	p-value	Remark
I (≥7METS)	45	10	0.02	Significant
II (5-6 METS)	59	10		
III (3-4 METS)	82	33		
IV (1-2 METS)	76	13		

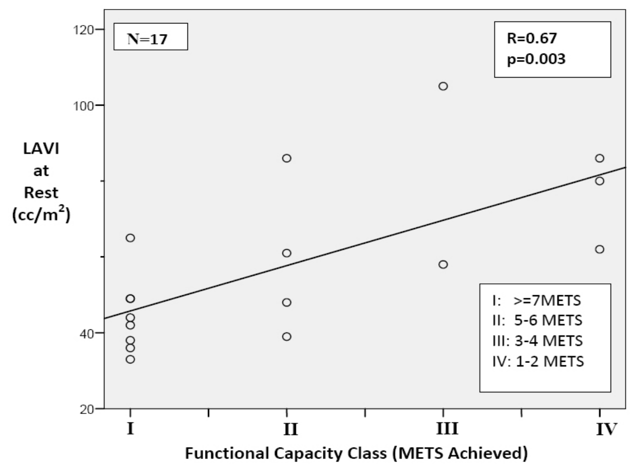


Figure 2. Correlation of Resting LAVI & Exercise Functional Capacity Based on METS Achieved (Spearman-Rank Correlation)

Table 5. Comparison of Resting LAVI & Peak Exercise Functional Capacity Based on Peak SPAP Achieved

Level of Peak Systolic PA Pressure (SPAP)	Resting LAVI Mean	SD	p-value	Remark
Good/ Class I (<60 mmHg)	44	12	0.02	Significant
Poor/ Class II (≥ 60 mmHg)	67	21		

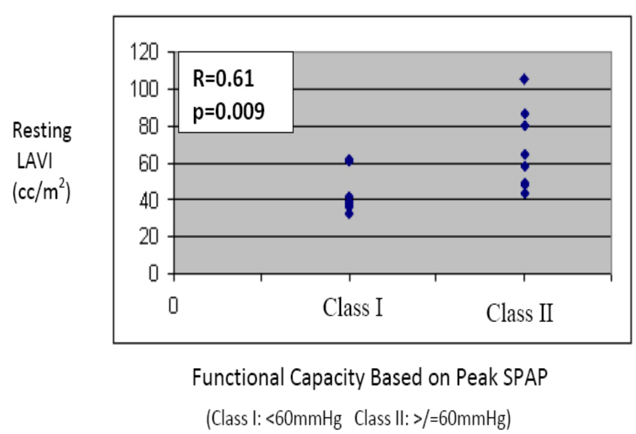


Figure 3. Correlation of Resting LAVI & Peak Exercise Functional Capacity Based On Peak SPAP Achieved

Table 6. Cut-off Values of Resting LAVI for Prediction of Exercise Functional Capacity Based on Peak SPAP

Resting LAVI cc/m²	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
≥65	50	100	100	58
≥60	50	71	71	50
≥50	60	71	75	56
≥45	90	71	82	83
≥40	100	57	77	100

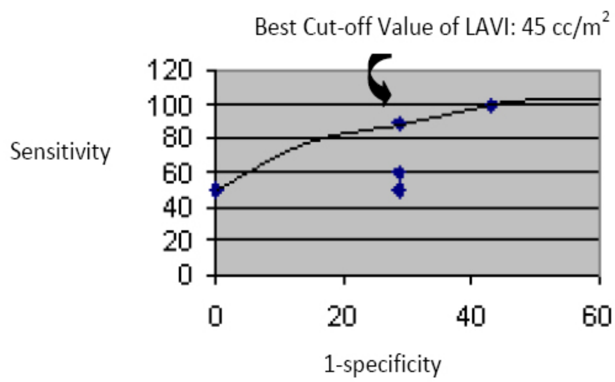


Figure 4. ROC Curve Showing Best Cut-off Point of LAVI That Predicts an Elevated SPAP >/60mmHg

Discussion

This study has investigated the value of LAVI in patients with rheumatic heart disease which had usually been an exclusion criterion from previous studies on LAVI. The degree of elevation of left atrial volume indices of these patients depends on the chronicity of left atrial pressure elevation which is likewise dependent on the severity of stenosis and mitral valve gradient. As shown in Figure 5, higher LA pressure has 2 effects namely a) higher degree of LA dilatation with consequent increase in LAVI and b) increase in pulmonary arterial pressure (PAP). We hypothesized that these two effects can mirror each other such that even a high PAP presenting as falsely low at rest can be unmasked by an elevated LAVI without further evaluation on TET. Since previous studies had already shown that as a measure of functional capacity in rheumatic MS with apparently low resting PAP, an increase in PAP >/=60mmHg on peak exercise mandates percutaneous intervention. Corollary to this, we considered LAVI as a surrogate marker of exercise functional capacity.

Previous studies on normal patients showed that the value of LAVI ranges from 16-28 cc/m2 (mean of 22). It was shown in this study that the mean LAVI in rheumatic MS was generally higher at 58 + 20 cc/m2 reflecting chronic exposure to higher LA pressure as discussed earlier. Elevation of MVG from mean of 10mmHg to 18mmHg at peak exercise has validated findings from prior studies that MVG is indeed an independent predictor of increased of SPAP.

There was good correlation between resting LAVI with functional capacity both assessed by METS and SPAP achieved (R=0.67 & R=0.61 respectively). LAVI <45 cc/m2 best predicted good functional capacity (Class I) via METS achieved (> 7 METS) and peak SPAP <60 mmHg with high sensitivity, PPV & NPV. Likewise, LAVI > 45 cc/m2 predicts lower functional class (Class II & above) as assessed by METS and SPAP > 60mmHg. This study has shown that an elevated LAVI parallels the degree of PAP increase in patients with rheumatic MS. In contrast to previous studies on LAVI on other subset of patients, this study has proven that higher LAVI is expected due to the hemodynamic features of mitral stenosis.

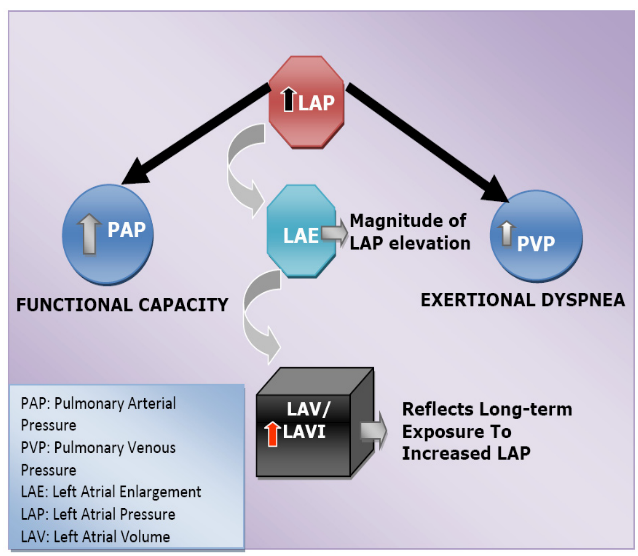


Figure 5. A Diagram showing LAVI as a Surrogate Marker of Elevated PAP

Limitation of the Study

We acknowledge the fact that although results were statistically significant, the small sample size materialized was due to stringent criteria in patient selection. Patients in sinus rhythm and atrial fibrillation should be separately analyzed.

Conclusion

Left atrial volume index (LAVI) predicts the exercise functional capacity of Rheumatic MS patients as objectively measured by METS and peak SPAP achieved on TET and Doppler stress echocardiography. As a surrogate marker of increased PAP, this measurement can be used in lieu of more expensive tests when functional capacity of patients with MS dictates a more definitive intervention.

Recommendations

It is strongly recommended that more patients be involved in this study in order to determine a more statistically significant cut-off value of LAVI that predicts exercise functional capacity measured by peak SPAP. It is noteworthy to find out what LAVI may predict functional capacity of rheumatic patients with concomitant multivalvular involvement.

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