Relationship between Left Atrial Function and Exercise Capacity in Patients with Dilated Cardiomyopathy

AHMED NASSAR, M.D.; ADEL GAMAL, M.D.; AYMAN MORTTADA, M.D. and ESSAM MOHAMED, M.Sc.*
The Department of Cardiology, Faculty of Medicine, Ain Shams University and National Heart Institute* Giza

Abstract
Evaluation of Left atrial (LA) function as well as left ventricular (LV) function in diseased hearts is very useful for clinical decision making particularly in heart failure.

Aim: This study aimed to assess the relation between LA function and exercise capacity in dilated cardiomyopathy (DCM) patients.

Methods and Results: The selected subjects were subdivided into 3 groups: Group 1: 10 healthy subjects, Group 2: 25 DCM patients with functional capacity 4 METS and Group 3: 15 DCM patients with functional capacity <4 METS. There was significant correlation between METS and each of LV diastolic function indices: A wave peak velocity \( (p<0.0001) \), E wave peak velocity \( (p<0.001) \), E/A ratio \( (p<0.0001) \) and mitral deceleration time (DT) \( (p-value<0.002) \), significant correlation between METS and each of the LA (maximum, minimum and pre-atrial systole) volumes \( (p<0.0001 \text{ for each parameter}) \). Also, we found significant correlation between METS and each of LA Total emptying Fraction, but not with LA emptying volumes \( (p<0.0001) \) and active emptying Fraction \( (p<0.0001) \), but not with LA passive emptying fraction.

Conclusion: LA emptying fractions are good tests for the assessment of diastolic function and functional capacity. Peak exercise capacity has a close correlation with LA function in heart failure, and it showed significant negative correlations with LA emptying volumes.

Key Words: Left atrial function – Exercise capacity – Dilated cardiomyopathy.

Introduction
THERE is increasing evidence that left atrial (LA) enlargement, as determined by echocardiography, is a robust predictor of cardiovascular outcomes [1].

Previous studies have demonstrated that left ventricular (LV) systolic function does not predict exercise capacity [2].

During ventricular diastole, LA is exposed to pressures of the LV. Augmentation of LA systolic function and active LA contribution to LV filling (booster pump function) is a common finding in conditions associated with LV diastolic dysfunction. Conversely, in dilated cardiomyopathy (DCM) attenuations of LA booster pump function and LA reservoir function have been observed. These attenuations are attributed to both altered LA loading conditions owing to LV diastolic dysfunction, and LA involvement in the myopathic process [3].

In particular, the use of standard echocardiography was very efficient to show that depression in LA systolic function occurs more in idiopathic than in ischemic DCM [4].

Patients and Methods
This prospective study enrolled 40 patients suffered from DCM and 10 normal control subjects. All Patients were recruited at the National Heart Institute.

The study was designed during the period from January 2010 to May 2011. The study protocol was reviewed and approved by our local Institutional Human Research Committee as it conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 2002.

Individuals in this study were subdivided into three groups:
- Group (1): Included 10 normal subjects as control.
- Group (2): Included 25 patients with functional capacity 4 METS
- Group (3): Included 15 patients with functional capacity <4 METS.
Inclusion criteria:

- All the patients included in this study had impaired LV systolic function (Ejection fraction (EF) 40%).
- All individuals were in sinus rhythm heart rate.

Exclusion criteria:

- Atrial fibrillation.
- Significant valvular heart disease.
- Unable to do exercise.
- Poor Echocardiographic quality.
- NYHA class IV heart failure (HF).

All individuals were evaluated by taking detailed history (smoking, diabetes mellitus, hypertension or ischemic heart disease. Symptoms, durations and medical treatments of HF and risk factors were also included in the history), a physical examination, Laboratory investigations (Lipid profile, kidney and liver function tests and Blood glucose level). ECG and trans-thoracic echocardiography were also done for all patients to assess chamber enlargement, ischemia and arrhythmias.

A- Assessment of LV systolic function:

- Using 2D-guided M-mode echocardiograms:

  LV dimensions including the thickness of posterior wall and ventricular septum were measured from 2D-guided M-mode. The measurements were obtained from the trailing edge of the septum to the leading edge of the posterior wall by using the parasternal long-axis acoustic window at the level of the LV minor axis, approximately at the mitral valve leaflet tips aligning the M-mode cursor perpendicular to the long axis of the LV [4].

- Using modified Simpson’s rule:

  The most commonly used 2D measurement for volume measurements is the biplane method of disks (modified Simpson’s rule). The principle underlying this method is that the total LV volume is calculated from the summation of a stack of elliptical disks. The height of each disk is calculated as a fraction (usually 1/20) of the LV long axis based on the longer of the two lengths from the 2- and 4-chamber views. The cross-sectional area of the disk is based on the two diameters obtained from the apical two and four chamber views [4]. This parameter is defined as the change in LV volume (i.e. stroke volume) divided by the initial volume (i.e. end-diastolic volume):

  \[ \text{Ejection fraction (EF)} = \frac{\text{EDV} - \text{ESV}}{\text{EDV}} \]

  Where EDV is end-diastolic volume and ESV is end-systolic volume [8].

B- Assessment of LV diastolic function:

  Trans-mitral flow velocity profiles were obtained from the apical 4-chamber view with the sample volume positioned at the tips of the mitral valve leaflets; peak early diastolic flow velocity (E-wave) and peak late diastolic flow velocity (A-wave) were measured from the trans-mitral flow velocity profile [6]. The deceleration time (DT) describes the time interval between the peak velocity and the point of intercept of the decay slope (or extrapolated slope) with the baseline [7].

C- Assessment of LA size and function:

- M-mode Echocardiography:

  The convention for M-mode measurement is to measure from the leading edge of the posterior aortic wall to the leading edge of the posterior LA wall. However, to avoid the variable extent of space between the LA and aortic root, the trailing edge of the posterior aortic is recommended [8].

  The LA size is measured at the end of LV systole when the LA chamber is at its greatest dimension [9].

- Two Dimensional Echocardiography:

  LA volume was measured using Simpson’s rule (monoplane), similar to its application for LV measurements; a standard apical 4 chamber view was obtained. The transducer was carefully angled to quantitavely maximize the LA size, and gain positions were adjusted to obtain the clearest outline of the endocardium. Special attention was focused on tracings of atrial chamber images. Thus, if atrial septum partially dropped out its location was approximated by reconstructing its image from the visualized view. Both the atrial appendage and pulmonary veins were carefully excluded. The largest LA size (Vmax) was traced at the beginning of the diastole at the opening of mitral valve, a straight line connecting both sides of leaflet base, at attachment of points to the valve ring, was taken as the border between ventricle and atrium. The smallest LA size [LA end systolic volume (Vmin)] was traced at ventricular end diastole, coinciding with R wave on the recorded ECG [10,11].

- LA function assessment:

  LA Passive Emptying Volume (PEV):

  It is defined as the difference between the maximum LA volume in early diastole (Vmax) and LA volume at the onset LA systole measured at the peak of p wave of simultaneously recorded ECG (Vp) [12]:

  \[ \text{PEV} = V_{\text{max}} - V_{\text{p}} \]
LA Passive Emptying Fraction (PEF):
It was defined as the ratio of passive emptying volume to maximum volume (Vmax) [11,12]:
\[
PEF\% = \frac{(V_{\text{max}} - V_P)}{V_{\text{max}}}
\]

LA Active Emptying Volume (AEV):
AEV was defined as the difference between the LA volume at onset of atrial systole (VP) and the minimum left atrial volume [13]:
\[
AEV = V_P - V_{\text{min}}
\]

LA Active Emptying Fraction (AEF):
LA pump function was defined as the ratio of active emptying (AEV) volume to the atrial volume at the onset of atrial systole (VP) [13]:
\[
AEF\% = \frac{(V_P - V_{\text{min}})}{V_P}
\]

LA Total Emptying Volume (TEV):
It is defined as the difference between the maximum LA volume in early diastole (Vmax) and the minimum left atrial volume [14]:
\[
TEV = V_{\text{max}} - V_{\text{min}}
\]

LA Total Emptying Fraction (TEF):
It was defined as the ratio of total emptying volume to LA maximum volume (Vmax) [14]:
\[
TEF\% = \frac{(V_{\text{max}} - V_{\text{min}})}{V_{\text{max}}}
\]

D- Exercise ECG protocol:
Patients were exercised on treadmill using the modified Bruce protocol. The exercise was symptom limited; it was terminated when patient developed dyspnea. The number of METs and exercise duration were recorded. Patients who developed typical anginal pain during exercise were excluded from the study. We considered 4 METs or more as an indication for good functional capacity, while less than 4 METs was as an indication for poor functional capacity.

Statistical analysis:
The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (SPSS 15.0.1 for windows; SPSS Inc, Chicago, IL, 2001). Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

Mean, Standard deviation (±SD), Minimum and maximum values (range) were used to describe numerical data while Frequency and percentage were used for non-numerical, data.

ANOVA test was used to assess the statistical significance of the difference between more than two study group means.

Post Hoc Test is used for comparisons of all possible pairs of group means.

Correlation analysis (using Pearson’s method) was used to assess the strength of association between two quantitative variables. The correlation coefficient denoted symbolically "r" defines the strength and direction of the linear relationship between two variables. Chi-Square test was used to examine the relationship between two qualitative variables.

Results
This cross sectional study was done at National heart institute in the period between January, 2010 and May, 2011. The study included 50 subjects; 31 males and 19 females with a mean age of 55 years. There was no statistically significant difference between the three groups regarding the gender (p>0.05). Patients in groups 2 and 3 showed no significant differences regarding their risk factors (p>0.05). Number of patients with NYHA class I and II were significantly higher in Group 2 (8 vs 0 and 15 vs 2 respectively; p=0.0001) while patients with NYHA class III were significantly higher in group 3 (13 vs 2; p=0.0001).

Echocardiographic characteristics in the study groups:
A- LV diastolic function indices:
Group 3 had the highest E-wave peak velocity, the highest E/A ratio 3, the lowest A-wave peak velocity, and the shortest mitral DT in comparison to group 1 and 2 with a high statistically significant difference in each (p<0.001) (Table 1).

B- LV volumes, dimensions and systolic function:
Group 3 showed the highest EDV, ESV, end diastolic dimension (EDD) and end systolic dimension (ESD) with high statistically significant differences in comparison to group 1 and 2.

Patients in group 1 had the highest LVEF which showed a high statistically significant difference (p<0.001) when compare to group 2 and 3, while there was no significant difference in LVEF between patients in group 2 and 3 (p>0.05) (Table 2).

C- LA volumes:
Maximal LA volume was measured at the onset of mitral valve opening, P-volume was obtained at the onset of atrial systole (P wave of ECG) while minimal volume was measured at mitral valve closure.
There was highly significant differences \( (p<0.01) \) between the three study groups regarding the Vol max (maximum LA volume) Vol. P (pre P wave LA volume) and Vol. min (LA minimum volume) (Table 3).

D- LA function indices :

The LA activity has 3 functions :

- LA reservoir function which was assessed by LA TEV and LA TEF.
- LA conduit function which was assessed by calculating the PEV and the PEF.
- The Booster pump function was assessed by calculating the AEV and the AEF. There were highly significant differences \( (p<0.01) \) between the 3 groups regarding the TEV and TEF, but there were no significant differences \( (p 0.05) \) regarding the PEF, the TEV and the PEV and. (Table 4).

Correlations:

- Correlation between LA function indices and functional capacity in METS:

Our study showed a highly significant positive correlation \( (p=0.001) \) between METS and each of TEF and AEF. However, this correlation was not significant between PEF and METS \( (p=0.068) \). The study also showed non-significant correlations between METS and each of TEV, AEV and PEV \( (p=0.518, p=0.197 \) and \( p=0.056 \) respectively).

- Correlation between METS and LA volumes :

There were highly significant negative correlations \( (p<0.001) \) between METS and maximum LA (Vol. max), pre atrial contraction (Vol.P) and LA minimum volume (Vol. min) \( (r=-0.578, -0.603, \) and \(-0.739 \) respectively).

Table (1): Comparison between three study groups as regards left ventricular diastolic function indices.

<table>
<thead>
<tr>
<th></th>
<th>Group 3</th>
<th>Group 2</th>
<th>Group 1</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>99.4</td>
<td>16.6</td>
<td>63.9</td>
<td>18.8</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A (cm/s)</td>
<td>40.3</td>
<td>12.1</td>
<td>71.6</td>
<td>19.2</td>
</tr>
<tr>
<td>E/A</td>
<td>2.7</td>
<td>0.8</td>
<td>1.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Mitral DT</td>
<td>111.3</td>
<td>28.0</td>
<td>212.9</td>
<td>52.8</td>
</tr>
</tbody>
</table>

DT: Deceleration time.
SD: Standard deviation.

Table (2): Comparison between three groups as regard left ventricular volumes, dimensions and systolic function.

<table>
<thead>
<tr>
<th></th>
<th>Group 3</th>
<th>Group 2</th>
<th>Group 1</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>212.0</td>
<td>154.8</td>
<td>25.3</td>
<td>0.001</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>77.0</td>
<td>27.0</td>
<td></td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>209.6</td>
<td>136.6</td>
<td>145.5</td>
<td></td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>154.8</td>
<td>77.0</td>
<td>27.0</td>
<td></td>
</tr>
<tr>
<td>EF (%)</td>
<td>26.1</td>
<td>7.4</td>
<td>5.9</td>
<td>0.001</td>
</tr>
<tr>
<td>EDD (cm)</td>
<td>7.0</td>
<td>0.9</td>
<td>6.4</td>
<td>0.001</td>
</tr>
<tr>
<td>ESD (cm)</td>
<td>5.8</td>
<td>0.9</td>
<td>5.3</td>
<td>0.001</td>
</tr>
</tbody>
</table>

EDV: End-diastolic volume.
ESV: End-systolic volume.
EF: Left ventricular ejection fraction.
EDD: End diastolic dimension.
ESD: End systolic dimension.
SD: Standard deviation.

Table (3): Comparison between three study groups as regard left atrium volumes.

<table>
<thead>
<tr>
<th></th>
<th>Group 3</th>
<th>Group 2</th>
<th>Group 1</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>VOL. max (ml)</td>
<td>72.2</td>
<td>60.8</td>
<td>25.2</td>
<td>0.009</td>
</tr>
<tr>
<td>VOL. P (ml)</td>
<td>53.7</td>
<td>42.9</td>
<td>19.6</td>
<td>0.003</td>
</tr>
<tr>
<td>VOL. min (ml)</td>
<td>46.3</td>
<td>29.6</td>
<td>16.0</td>
<td>0.001</td>
</tr>
</tbody>
</table>

VOL max: Maximum LA volume.
VOL p: Left atrial volume at peak of ECG P wave.
VOL min: Left atrial minimum volume.
SD: Standard deviation.

Table (4): Comparison between three study groups as regard LA function indices.

<table>
<thead>
<tr>
<th></th>
<th>Group 3</th>
<th>Group 2</th>
<th>Group 1</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEF</td>
<td>36.5</td>
<td>53.2</td>
<td>9.0</td>
<td>0.001</td>
</tr>
<tr>
<td>AEF</td>
<td>15.5</td>
<td>34.5</td>
<td>10.8</td>
<td>0.001</td>
</tr>
<tr>
<td>PEF</td>
<td>26.1</td>
<td>28.5</td>
<td>7.8</td>
<td>0.10</td>
</tr>
<tr>
<td>TEV (ml)</td>
<td>25.9</td>
<td>31.2</td>
<td>10.0</td>
<td>0.054</td>
</tr>
<tr>
<td>AEV (ml)</td>
<td>12.5</td>
<td>14.4</td>
<td>5.6</td>
<td>0.051</td>
</tr>
<tr>
<td>PEV (ml)</td>
<td>18.4</td>
<td>16.8</td>
<td>6.1</td>
<td>0.394</td>
</tr>
</tbody>
</table>

TEF: Total emptying fraction.
AEV: Active emptying volume.
AEF: Active emptying fraction.
PEF: Passive emptying volume.
SD: Standard deviation.
TEV: Total emptying volume.

- Correlation between LV diastolic function indices and METS:

The study showed highly significant negative correlations \( (p<0.001) \) between E-wave velocity and E/A ratio with METS \( (r=-0.573 \) and \(-0.591 \) respectively). The METS also had highly significant positive correlations \( (p<0.01) \) between A-wave velocity and mitral DT \( (r=0.490 \) and 0.473 respectively) (Fig. 1).
Discussion

LA volume provided powerful prognostic information that is independent of and incremental to cardiopulmonary exercise testing in patients with chronic HF due to LV systolic dysfunction [15]. In the present study, left atrial TEF was found to be higher in patients with functional capacity 4 METS. There was a positive correlation between each of TEF and AEF and the functional capacity of patients. Terzi and his colleagues [16] signed agreements with our results, though they could not separately examine the contributions of passive and active atrial emptying to LV filling. They also found significant difference between their study groups regarding LA volume which is compatible with our results. It should be noted that they assessed the LA parameters using the LA systolic volume index (LAV max/BSA) and LA end diastolic volume index (LAV min/BSA).

Regarding left ventricular ESD, EDD, EDV and EF, our results did not show similarity to what Terzi, et al. [16] mentioned in their study; they found LVEF to be significantly higher in the group of patients who had peak VO2 >14ml/Kg/min in comparison to the other group who had peak VO2 14ml/Kg/min (p <0.05), while the E-wave peak velocity and the E/A ratio were not statistically significant between the 2 groups. The A-wave peak velocity was found in to be significant in differentiation between their two study groups and this was compatible with our results. The differences in the results between our study and the study done by Terzi and his colleagues [16] might be attributed to their different method in classifying their study groups by using the cardiopulmonary exercise testing to assess the functional capacity.

In our study we found that METS had a significant negative correlation with E-wave peak velocity ($p=0.0001$), and a significant positive correlation with A-wave peak velocity ($p=0.001$). These showed some differences with the results of Terzi, et al. [16] who showed the peak VO2 to have no significant correlation with E-wave peak velocity ($p=0.29$), but a significant correlation with A-wave peak velocity ($p=0.009$).

The results of the present study demonstrate that LA function at rest is related to exercise performance in ischemic cardiomyopathy (ICM) and DCM. We observed that functional capacity was directly related to LA-EF (total and active). Also, we observed that A wave peak velocity, E wave peak velocity, E/A ratio and mitral-DT correlated well with peak exercise performance. Also, we found significant negative correlation between peak exercise capacity and LA volumes (maximum, minimum and pre-atrial contraction volume). There are several mechanisms that explain the relationship between exercise capacity and LA function. LA function reflects LV diastolic filling and therefore predicts the cardiac output and stroke volume response to exercise [17]. The reduced LA function may contribute to a decrease in LV preload and stroke volume according to the Frank-Starling mechanism [13]. In a study done by Smart, et al. [18] on 155 patients with congestive HF, they reported association of diastolic rather than systolic function with functional capacity, which may have reflected the limitations of EF. So, the functional capacity appears related not only to diastolic function, but also to systolic function and filling pressure, and is most closely associated with a combination of these factors.

Conclusion:

LA function is associated with LV diastolic filling and cardiac output response to exercise. The LA emptying fractions are good tests for assessment of diastolic function and functional capacity. Peak exercise capacity has a close correlation with LA function in heart failure; furthermore, it showed significant negative correlations with LA emptying volumes. Peak exercise capacity also correlates well with E-wave velocity, A-wave peak velocity, deceleration time and E/A ratio. Multi-center studies using the same protocol and examining a larger number of patients are needed.

Limitations of the study:

We investigated patients with HF (EF 40%) due to DCM (idiopathic and ischemic) but we excluded patients with other causes of HF. We also...
excluded patients with less severe systolic dysfunction, patients with NYHA functional class IV and those with severe mitral regurgitation. Thus, our conclusions may not apply to those groups of patients and to patients who have LV impaired diastolic function with preserved systolic function. Our findings are based on a single center study with a relatively small sample size of the cohort. Multi-center studies using the same protocol and examining a larger number of patients are needed. Moreover, cardiopulmonary exercise testing was not available.

References