Investigating the European Society of Cardiology Diastology Guidelines in a practical scenario

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Aims Recently, the European Society of Cardiology (ESC) released a consensus statement for the diagnosis of heart failure with preserved ejection fraction (HFPEF). It state that $E/e'$ > 15 or < 8 clearly define those with or without HFPEF and that for those in the range 8–15, other parameters should be examined.

Methods and results We retrospectively analysed 1229 consecutive echocardiograms (57% males) for the utility of echocardiographic measures including left atrial volume index (LAVI), left ventricular mass index (LVMi), and pulmonary venous and mitral inflow Doppler. LAVI of 40 ml/m² provided the greatest sensitivity and specificity of 76 and 77%, respectively, with reference to $E/e'$ for the detection of diastolic dysfunction. The ESC definition of raised LVMi yielded a sensitivity and specificity of 32 and 99%, respectively. We found that the mitral and pulmonary inflow provided little incremental information. These results remained consistent between those with normal and abnormal ejection fraction.

Conclusions There appears to be little incremental value of pulmonary and mitral Doppler measures beyond the measure of mitral $E$ wave. An LAVI cut-off of 40 ml/m² maximizes both sensitivity and specificity. However, ESC guidelines of raised LVMi in patients with HFPEF would appear to heavily trade sensitivity for specificity.

Introduction

The accurate assessment of diastolic function has been an increasingly important component of a complete echocardiographic study, especially since the evolution of understanding that isolated systolic dysfunction probably accounts for less than half of patients with symptomatic heart failure. In a prospective evaluation, Bursi et al.¹ examined 556 consecutive cases of heart failure in Olmsted county, Minnesota. They concluded that more than half (55%) of patients have heart failure with preserved ejection fraction (HFPEF). Diastolic dysfunction was present in 80% of all cases, combined systolic and diastolic dysfunction was present in 37%, and isolated diastolic dysfunction was present in 44%. Additionally, HFPEF was associated with a high mortality rate, and not significantly different when compared to that of patients with reduced ejection fraction (EF). This was in contradistinction to earlier reported studies suggesting that HFPEF was a less malignant syndrome.²,³ Predisposing conditions for HFPEF are older age, female gender, diabetes and obesity, arterial hypertension, and left ventricular (LV) hypertrophy.⁴,⁵

Recently, a consensus from the Heart Failure and Echocardiography Association of the European Society of Cardiology⁶ proposed new diagnostic criteria for diastolic heart failure centred around the measurement of the $E/E'$ ratio. The peak early diastolic mitral $E$ velocity is influenced by the pressure in the left ventricle and atrium and LV relaxation, whereas the $E$ velocity at the mitral annulus is regarded as a non-invasive surrogate for LV relaxation. The combination of the two measures is assumed to overcome the influence of ventricular relaxation on the peak $E$ velocity and to reflect left atrial pressure.⁷ This $E/E'$ ratio is a powerful predictor of survival after myocardial infarction. Indeed, values > 15 are prognostically more important than clinical or other echocardiographic variables.⁸ The close correlation between $E/E'$ and LV filling pressures has been confirmed in heart failure patients with low or normal EFs.⁹ An $E/E'$ ratio of < 8 reflects normal LV filling pressures.¹⁰

The European guidelines states that an $E/E'$ ratio > 15 in the presence of preserved EFs in a patient with heart failure symptoms is diagnostic of HFPEF. A ratio of < 8...
essentially excludes the presence of HFPEF. However, if this ratio is between 8 and 15, this may be suggestive of diastolic dysfunction, but other echocardiographic measures should also be used to support this diagnosis. These include measures of LV mass index (>122 and >149 g/m² in women and men, respectively), left atrial volume index (LAVI), mitral inflow Doppler (deceleration time > 280 ms), and pulmonary venous inflow Doppler (Ar – Ad > 30 ms). Non-echocardiographic investigations include an electrocardiogram demonstrating atrial fibrillation or raised plasma natriuretic peptides.

In patients with a well-established history of heart failure, there is clear evidence that concentric LV remodelling (with a high LV wall mass–volume ratio) has important implications for the diagnosis of HFPEF and is a potential surrogate providing evidence of diastolic LV dysfunction. Indeed, one unifying hypothesis has suggested that the principal difference between HFPEF and systolic heart failure is the degree of LV remodelling or dilatation, as 3D volumetric echocardiography has demonstrated that early stages of remodelling occur in the HFPEF population. Hence it has been included as a diagnostic minor criterion in the European recommendations (measures of LV mass index >122 and >149 g/m² in women and men, respectively) and can be considered sufficient evidence of diastolic dysfunction when the E/e’ is in the equivocal range 8–15.

Left atrial volume indexed to body surface area (LAVI) was first recognized in the elderly as a strong predictor of cardiovascular events, more so than other echocardiographically derived measures such as LV mass index. LAVI, in patients with suspected heart failure and normal LV systolic function, is a powerful independent predictor of LV diastolic dysfunction as predicted by serum N-terminal pro-B-type natriuretic peptide (NT-proBNP). Its adds incremental value and diagnostic precision in the evaluation of patients with suspected diastolic heart failure.

Combinations of various Doppler measures have also been proposed to diagnose diastolic LV dysfunction, in particular, the combined use of mitral and pulmonary venous inflow, measuring the difference between the duration of reversed pulmonary vein atrial systolic flow (Ar) and the duration of mitral A wave flow (Ad) (Ar – Ad > 30 ms). This has been included as an echocardiographic criterion in early guidelines and has been kept in the latest European Consensus document. However, it suggests that the use of these Doppler measures is no longer recommended as a first-line diagnostic approach to diastolic LV dysfunction, and should only be considered when tissue Doppler velocities are suggestive but non-diagnostic.

In our retrospective study, we sought to apply the new European Consensus statement on the diagnosis of HFPEF to an unselected population of patients attending out tertiary centre echocardiography laboratory and to assess the relative contribution of the measures suggested in the routine assessment of diastology.

Material and methods

A total of 1229 consecutive echocardiograms (697 males) were included in our retrospective study. These were performed in our high-volume tertiary referral echocardiography laboratory over an approximate period of 17 weeks (25 January - 1 June 2007). Only patients with severe valvular disease, heart transplantation (due to enlarged atria secondary to the atrial anastomosis), and atrial fibrillation, and those with highly focused/limited studies were excluded.

All studies were performed with a Hewlett-Packard Sonos 5500, equipped with harmonic imaging, 4.2 MHz transducer, and tissue Doppler imaging. Standard imaging techniques were used to obtain all views. The analysis of all echocardiographic data was completed offline, using the Xcelera reporting package, with measurements performed independently by authors I.J. and W.T.E. These included left atrial (LA) parasternal long-axis dimension, 2- and 4-chamber LA area, 4-chamber LA volume, and shortest longitudinal LA length [for calculation of the LA volume index by the biplane area–length method, LV mass index was automatically calculated by the software by the following formula recommended by the American Society of Echocardiography: LV mass index = [0.80(LVEDD+IVS+PW) – LVEDD²]/BSA], where LVEDD is the LV end-diastolic dimension, VS the ventricular septum thickness, PW the posterior wall thickness, and BSA the body surface area. Doppler measures included those of pulsed wave mitral inflow: E and A wave peaks, where A is the wave duration and E the wave deceleration time. Tissue Doppler was taken for septal and lateral early (e’) and late (a’) peak annular velocities. Finally, pulmonary inflow velocities including late systolic peak (S2), diastolic peak (D), and A reversal (Ar) along with A reversal duration (ArD) were recorded.

Statistical analysis

All statistical analyses were performed using SPSS 15.0 for Windows. Paired t-tests were conducted to determine interobserver variability between the two recorders. Correlations of echocardiographic measures with E/e’ were investigated using univariate and multivariate linear regression analyses and by expressing the sensitivity/specificty via the area under the receiver operating characteristic curve, with a value of E/e’ > 15 used to define diastolic dysfunction.

Results

This study encompassed 1229 all-comers (56.9% males, mean age of 61 years, SD 17.6), with a wide range of study indications to our tertiary referral echocardiography laboratory; demographic and clinical information along with test indication were pragmatically limited to those which we were able to abstract from the echocardiography report (Table 1). Of note, there was no significant interobserver variability (all: P > 0.05) among the abstracted echocardiographic measures.

The utility of each of the echocardiographic measures in the assessment of diastolic function was addressed sequentially by examining its predictive performance in comparison to E/e’.

Left atrial volume index

Most measures were obtained successfully in more than 80% of subjects, with the highest success for mitral inflow Doppler (Table 2). However, there was a comparatively low rate (59%) of acquisition of the parasternal 2-chamber LA area and consequently the biplane area–length LA volume estimate (55%). This was not felt due to the image quality/technical factors, but due to its lack of inclusion in a formal protocol at the time, as prior to April 2007, we were routinely using the prolate ellipse method of LA volume estimation which does not require 2-chamber measurements. In order to ascertain whether the lack of availability of the 2-chamber LA area influenced overall results and their applicability, we compared the 2 groups
of patients having ‘normal’ or abnormal LAVI in the \(E/e' > 15\) and \(< 8\) groups (24 and 23%), respectively. This LAVI of 40 ml/m² cut-off yielded a sensitivity of 76% and a specificity of 77% based on normal \((E/e' < 8)\) or abnormal \((E/e' > 15)\) diastolic function, with higher LAVIs resulting in gains in specificity but concomitant loss of sensitivity (and vice versa for lower LAVIs).

**Left ventricular mass index**

Left ventricular mass index (LVMI) estimation is reliant on the end-diastolic measurements of LV posterior and septal wall thicknesses and internal dimension in addition to body surface area. These measures were successfully acquired in 92% of patients, with a high LVMI (based on males >149 g/m² and females >122 g/m²) seen in 2, 9, and 15% of those with \(E/e'\) of \(< 8\), 8–15, and >15, respectively. This yielded an overall specificity of 99%, but a low sensitivity of 32%, based on abnormal \((E/e' > 15)\) or normal \((E/e' < 8)\) diastolic function, respectively. If the cut-off for abnormal LVMI index is taken as the lower limit of the mildly abnormal range (males >116 g/m² and females >96 g/m²), specificity and sensitivity become 61 and 88% and a high LVMI is seen in 12, 24, and 61% of those with \(E/e'\) of \(< 8\), 8–15, and >15, respectively. We further examined subpopulations, according to gender and normal EF, and examined these two LVMI cut-offs. The results are detailed in Figure 1.

We further examined the incremental use of LAVI and LVMI when both the measures are used for the definition of HFPEF. In those with \(E/e' > 15\), only 23% of patients had both increased LAVI and LVMI according to the proposed criteria. However, with application of the lower cut-offs for LVMI as detailed above, this increases to 53.3%. Conversely, in patients with \(E/e' < 8\), 75.8% had both normal LAVI and LVMI, and this was minimally affected by lowering the LVMI threshold further (70.5%). The two thresholds for LVMI are similarly explored in the patients with \(E/e' < 15\) in Figure 2.

Following the flow chart detailed in the consensus document for exclusion of HFPEF (which relies on all these diastolic measurements being within normal limits), we were able to exclude the diagnosis in 102 patients (7.9%).

**Difference between durations of reversed pulmonary venous atrial systolic flow and mitral A wave**

\(A_d\) and \(A_d\) were successfully recorded in 90 and 57% of patients, respectively, with the combination of measures also successfully attained in 57%. An \(A_d - A_d\) of greater than 30 ms was seen in 3, 4, and 1% of those with \(E/e'\) of \(< 8\), 8–15, and >15, respectively, with resulting sensitivity of 3% and specificity of 97%.

**Mitral inflow**

Mitral inflow Doppler was recorded successfully in 98–99% of patients. The European Consensus document suggests that a mitral inflow \(E/ A < 0.5\) with an \(E/e'\) deceleration time \(> 280 \text{ ms}\) in patients over the age of 50 years is a minor criterion for the diagnosis of HFPEF. In our total population, we had six patients who fulfilled these three criteria, with 1% or less in each of the three \(E/e'\) groups. This yielded a sensitivity of 1% and specificity of 99%.
These values are clearly representative of mild diastolic dysfunction. However, this early stage of diastolic dysfunction may correlate less well with LAVI, LVMi, E/e', and LVEDP than later stages when the A wave velocity is reduced along with the deceleration time (pseudonormalization and restrictive stages of diastolic dysfunction). We feel a more sensitive, although less specific use of the mitral inflow, may be the response to Valsalva and/or measurement of a shortened deceleration time. Alternatively, the well-recognized grades of diastolic dysfunction, based on the mitral inflow Doppler could be incrementally weighted to aid the diagnosis of HFPEF.

The measurement of $A_d - A_{d0}$ was successfully attained in 57% patients. This is in concordance with previous observations that suggested that pulmonary venous inflow is often recorded less successfully (49–84%) than other diastology measures. Additionally, these authors conclude that pulmonary venous inflow takes longer time to obtain and has more inter-reader variability than mitral valve (MV) inflow and annular tissue Doppler. In our population, as with the specific mitral inflow criterion, we had very few patients with $A_d - A_{d0} > 30$ ms, and the measure had minimal sensitivity. For all these reasons, again we feel that it has little to contribute to overall diastolic functional assessment.

In our population, the biplane area-length LAVI was attained in only 55% of patients, largely as a result of a reliance on the prolate ellipse method of LAVI calculation for the first 3 months of our collection. However, this did not appear to introduce a selection bias. The mean LAVI, in all three $E/e'$ groups, was above the upper limit of normal, but the 40 ml/m² cut-off suggestion, correlating to the lower limit of severely enlarged, appeared to maximize both sensitivity and specificity. In patients with systolic dysfunction, the LAVI was increased across all $E/e'$ subgroups, but sensitivity and specificity were unchanged. The association of diastolic dysfunction with systolic dysfunction has been previously recognized. In fact, combination of EFs and LAVI has been suggested for practical application in the assessment of diastolic dysfunction.

The reference values suggested in the consensus document for LVMi for conformation of diastolic dysfunction are also the lower limits of severe, with cut-offs of >149 and >122 g/m² in males and females, respectively. We found this to pick up comparatively few patients, being highly specific (98%), but poorly sensitive (35%). We applied a different cut-off, defining patients with a high LVMi as those with a value greater than the upper limit of the normal range (>116 and >96 g/m² for males and females, respectively). This yielded a much higher number of patients, although with a corresponding drop in specificity.

### Table 3. Normal and impaired systolic function: number of patients with abnormal diastolic measures in the three main $E/e'$ categories

<table>
<thead>
<tr>
<th>LVEF</th>
<th>$E/e'$</th>
<th>LAVI (ml/m²)</th>
<th>High LV mass index (g/m²)</th>
<th>$A_d - A_{d0}$ (s)</th>
<th>$E/A &lt; 0.5$, DT &gt; 280 ms, and age &gt; 50</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;40</td>
<td>≤40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50%</td>
<td>&lt;8</td>
<td>53</td>
<td>174</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>8-15</td>
<td>74</td>
<td>120</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&gt;15</td>
<td>23</td>
<td>7</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>≤50%</td>
<td>&lt;8</td>
<td>6</td>
<td>20</td>
<td>1</td>
<td>0</td>
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<td></td>
<td>8-15</td>
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<td>25</td>
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<td>&gt;15</td>
<td>15</td>
<td>5</td>
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greater sensitivity, but with little decrement in specificity. Similar to LAVI, LVMI values in those with systolic dysfunction were higher in all $E/e'$ categories.

The combination of the LVMI and LA volume has been examined by Melenovsky et al. who found that the product of LVMI and maximal LA volume best identified HFPEF patients. The inter-dependency between the two measures has also been examined with high LVMI predictive of those with high LAVI. We also demonstrated the association of LVMI with LAVI (53% of those with $E/e' > 15$ have

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**Figure 1** Sensitivity ($E/e' < 8$) and specificity ($E/e' > 15$) of left ventricular mass index (LVMI) based on current consensus cut-offs ($>149$ g/m$^2$ in men and $>122$ g/m$^2$ in women) and proposed cut-offs ($>116$ g/m$^2$ in men and $>96$ g/m$^2$ in women) are explored in males and females. (A) Left ventricular ejection fraction (LVEF) $>50\%$ and (B) LVEF $\leq 50\%$. 

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both indices elevated; 76% with E'/e' < 8 have both indices within reference range).

**Study limitations**

Our study is retrospective, and limitations include lack of clinical data (with the exception of that on the request form), absence of LV end-diastolic volume index recording, and non-availability of NT-proBNP. Consequently, we may have over-estimated the numbers we have labelled as having diastolic dysfunction. However, we feel that it is representative of the real-world situation that have clearly demonstrated the lack of utility of Ard and the mitral inflow Doppler E/A, 0.5 with deceleration time. For patients with preserved systolic function, these guidelines may also be appropriately applied to those with systolic dysfunction.

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**References**


