Increased left atrial volume index is an independent predictor of raised serum natriuretic peptide in patients with suspected heart failure but normal left ventricular ejection fraction: Implication for diagnosis of diastolic heart failure

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Abstract

Background: Left atrial volume index (LAVI) is increasingly recognised as a relatively load-independent marker of left ventricular (LV) filling pressures. We assessed the capacity of LAVI to predict LV diastolic dysfunction in comparison with N-terminal pro B-type natriuretic peptide (NTproBNP) in patients with suspected heart failure and a normal ejection fraction (EF).

Methods: 137 patients with suspected heart failure (HF), referred from the community for echocardiography, prospectively underwent Doppler echocardiography, LAVI and NTproBNP estimation. Raised LAVI and reduced LV systolic function were defined as >26 ml/m2 and LV EF <50% respectively.

Results: Of 137 patients, 21 were excluded (2 with significant mitral valve disease and 19 with atrial fibrillation). Of the remaining 116 subjects, 92 showed normal LV systolic function. The univariate predictors of serum log NTproBNP were age (p<0.001), LA dimension (p=0.001), LAVI (p<0.001), A wave (p=0.001), E:A (p=0.07) and septal wall thickness (p=0.004). However on multivariate analysis, LAVI was found to be the most consistent and significant predictor of NTproBNP. The area under the curve of the receiver operating characteristic (ROC) curve for NTproBNP in detecting patients with LVEF ≥50% and LAVI >26ml/m2 was 0.81 (p<0.0001) and for patients with LAVI >26ml/m2 with and without LVEF ≥50% was 0.82 (p<0.0001).

Conclusion: This data confirms that LAVI on resting echocardiography, specifically in patients with suspected HF and normal LV systolic function is a powerful independent predictor of LV diastolic dysfunction as predicted by serum NTproBNP. In a population with a high suspicion of diastolic heart failure, LAVI may significantly contribute to diagnostic precision.

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Keywords: Diastolic dysfunction (DD); Diastolic heart failure; Transmitral Doppler; Tissue Doppler Imaging (TDI); N-terminal pro B-type natriuretic peptide (NTproBNP); Left atrial volume (LAVI); Left atrial volume index (LAVI)

1. Introduction

While controversy persists regarding the exact pathophysiology and indeed the nomenclature of diastolic ventricular dysfunction (DD) [1,2], its existence is now well established. At least 30% of all patients exhibiting features of heart failure have a left ventricular ejection fraction (LVEF) of >50% [3–8]. The clearest associations with DD are: its increasing prevalence with age [9,10], diabetes mellitus, left ventricular hypertrophy, systemic hypertension, myocardial ischemia and renal dysfunction. Moreover, the prognostic implications of DD are severe with annualised mortalities ranging from 5% to 8% [8].

Despite the recognition of DD as a condition in which isolated or a combination of an abnormal active relaxation (r) or passive filling (end-diastolic pressure—volume relationship—EDPVR) is exacerbated by dynamic neurohor-
monal loading [1], it has proved difficult to agree on a non-invasive technique to identify those with consequently raised LV filling and left atrial pressures (LAP). This is particularly clinically pertinent to those with suspected heart failure with a grossly normal ejection fraction, i.e. patients with isolated diastolic heart failure (DHF). Pragmatically, a number of guidelines have emphasised the role of coupling heart failure with a normal LVEF with transmitral Doppler [12–14]. Although a classification system based on transmitral Doppler has been well-validated in those with an impaired systolic function and DD [15], in those with a normal LVEF it has implicit shortcomings resulting from being a load-dependent point estimate of filling pressures [16,17]. While novel techniques such as tissue Doppler imaging (TDI) combined with transmitral Doppler have been advocated, these too suffer from a low sensitivity (in some series E/Ea >15 has a sensitivity of <50% for raised LAP) in those with heart failure but a normal LVEF [18,19]. A clinical mandate therefore exists to identify a more accurate parameter to assess diastolic heart failure.

We and others have previously reported the association between left atrial volume (LAV) and cardiovascular events [20–22]. Since the LA communicates with the LV through an open mitral valve orifice in diastole, increased LV filling pressure raises wall tensions and results in LA distension [23]. While 2D LA dimensions are technically easy to measure, LAV has been proposed as a potentially better index of LA enlargement since LA remodelling is associated with a reduced sphericity, facilitating LAV derivation from 2D parameters. LAV may represent an integrated assessment of chronic LV filling pressures, obviating the need to rely on point Doppler estimates that are subject to loading variation.

Therefore, we prospectively examined the relationship between LAV indexed to body surface area (LAVI) and N-terminal pro B-type natriuretic peptide (NTproBNP) as a marker of DD, in patients with suspected heart failure but a normal LVEF i.e. DHF. NTproBNP is secreted from the ventricles and to a lesser extent the atria in response to volume expansion and wall stretch; it has been extensively validated in LV systolic dysfunction [24] and has been shown to be sensitive (>85%) for DD in a population similar to ours [25].

2. Methods

2.1. Patient selection

Patients referred to our community echocardiography service with symptoms and signs of heart failure underwent venesection for serum NTproBNP and electrocardiography (ECG). An abnormal ECG is defined as presence of atrial fibrillation or flutter on resting ECG or significant mitral valve disease on 2D echocardiography were excluded. Clinical signs of heart failure were defined as presence of at least one of the following: raised jugular venous pressure, peripheral oedema, hepatomegaly, basal inspiratory crepitation or gallop rhythm. The research ethics committee approved the study.

2.2. Natriuretic peptides

Prior to echocardiography, blood was taken from the subjects in biochemistry gel serum separation tubes, allowing to clot, centrifuged and serum separated and stored at −20 °C for 24 h and then −70 °C until analysis. Serum NTproBNP levels were analysed in an independent laboratory, blinded to the echocardiographic data using an Elecsys 2010 (Roche Diagnostics, Lewes) [26]. The interassay percentage coefficient of variation is 3.2% at 20.7 pmol/l, 2.9% at 41.9 pmol/l, 2.6% at 126 pmol/l, 2.3% at 586 pmol/l, with detection limit of 0.6 pmol/l and upper measuring limit of 4130 pmol/l.

2.3. Echocardiography

Echocardiographic images were acquired in the standard parasternal and apical views by 1 of 5 experienced sonographers using the Cypress (Acuson, Mountain View, California) ultrasound system. LVEF was assessed by using a 2-dimensional visual estimate method. This form of qualitative assessment of LVEF by an experienced observer is comparable to trackball measurement which was also demonstrated by our department [27]. Normal LVEF was defined as an estimated visual ejection fraction of greater or equal to 50%. For measurement of left ventricular diastole filling pattern, sample volume of pulse Doppler was placed at the tip of mitral valves. From the transmitral recording, peak E velocity (peak early transmitral filling velocity during early diastole) and peak A velocity (peak transmitral atrial filling velocity during late diastole) were measured in centimetres per second. Thereafter, the ratio of E and A wave was calculated. Deceleration time (DT) of the E wave was also calculated as the time elapsed between peak E peak velocity and the point where the extrapolation of the deceleration slope of E velocity crosses the zero baseline measured in milliseconds. A total of three left atrial dimensions were obtained at end-systole from parasternal long axis (D1) and apical four-chamber view (horizontal [D2] and anteroposterior measurements [D3]). LA volume was calculated using the formula for an ellipsoid [28]:

\[
\text{LA volume (ml)} = \pi/6(D_1 D_2 D_3)
\]

where \(D\) is the LA dimension from the aforementioned measurements. LAVI was calculated as LA volume/body surface area (BSA). The normal value of LAVI was
reported as 20±6 ml/m² [29]. In our study, we used one standard deviation above the mean to define upper limit of LAVI which is 26 ml/m². The left ventricular wall thickness was measured as interventricular septal thickness (IVST) and posterior wall thickness (PWT) at end-diastole in the parasternal long or short axis view. Severity of mitral valve regurgitation assessment was based on colour flow imaging and Doppler assessment. Presence of mitral stenosis was defined as mitral valve area of <2.5 cm² using continuous wave pressure half-time across LV in flow.

3. Statistical methods

Results from normally distributed continuous data are shown as mean±S.D. Shapiro and Francia’s W test of normality was performed to investigate whether variables were approximately normally distributed. A natural log transformation was used to improve the normality assumption for serum NTproBNP and LAVI. Univariate predictors of serum NTproBNP were assessed using linear regression analysis. Multivariate analysis was then performed by entering into model variables that were considered significant on univariate analysis. In addition, receiver operating characteristic (ROC) curves were produced for the serum NTproBNP to predict LA VI. A p value of <0.05 (two-sided) was considered significant. Statistical analysis was performed with Analyse-it software for Microsoft Excel (Version 1.62, Analyse-it software Ltd., Leeds, United Kingdom) and Stata statistical software (version 7, StaStatCorp, USA).

4. Results

4.1. Patients

Of the 137 patients referred, 19 patients had evidence of atrial fibrillation (AF) or flutter on resting ECG and 2 patients had evidence of significant mitral regurgitation on echocardiography and they were excluded from the study. Of the remaining 116 patients, 24 (21%) and 22 (19%) patients demonstrated LVEF <50% and LAVI >26 ml/m² respectively. The characteristics of the 92 patients with LVEF ≥50% are shown in Table 1. Accordingly, 48% of these patients demonstrated signs of HF and almost half of them were on diuretic therapy. Abnormal ECG was noted in 45% of the patients.

4.2. Univariate predictors of serum NTproBNP

Amongst the clinical variables, only age was found to be a significant predictor of serum NTproBNP. LVEF was not a significant predictor of NTproBNP in this group of patients. However, other echocardiographic variables such as the LA dimension, LAVI, transmitral Doppler in-flow parameter (A wave) and LV septal wall thickness were significant predictors of NTproBNP (Table 2).

4.3. Independent predictors of NTproBNP

Amongst clinical and echocardiographic variables, LAVI and age were the only independent predictors of NTproBNP. The ratio for age and LAVI were 1.28 (p=0.003) and 2.81 (p<0.001) respectively (Table 3). Older patients were found to have higher values, with a 10 year increase in age associated with an increase in NTproBNP of almost 30%. On the other hand, an increase of one-unit in LAVI (on the natural log scale) results in the serum NTproBNP increasing by nearly 3-fold. Fig. 1 shows scatter plot of logeNTproBNP versus logeLAVI demonstrating a significant correlation (rs statistic =0.5, p<0.0001).

4.4. Predictors of LAVI in patients with LVEF ≥50%

Amongst clinical and echocardiographic variables, age (p<0.001), heart rate (p=0.04), interventricular septal thickness (p<0.001), posterior wall thickness (p<0.001),...
LV mass index \( (p < 0.001) \) and deceleration time of E wave \( (p = 0.07) \) were found to be the univariate predictors of LA VI. However, the independent predictors of LA VI were age \( (p < 0.001) \), posterior wall thickness \( (p = 0.003) \), diabetes mellitus \( (p = 0.07) \) and deceleration time of E wave \( (p = 0.02) \). Area under the curve (AUC) of ROC curve for the prediction of \( \text{LAVI} > 26 \text{ ml/m}^2 \) by NTproBNP was 0.81 in patients with LVEF \( \geq 50\% \) \( (\text{Fig. 2A}) \) which was not dissimilar in patients with and without LVEF \( \geq 50\% \) \( (\text{Fig. 2B}; \text{Tables 4 and 5}) \).

4.5. Prevalence of diastolic heart failure

If \( \text{LAVI} > 26 \text{ ml/m}^2 \) is taken as the cut off for the prediction of DD in patients presenting with symptoms and signs of heart failure and LVEF \( \leq 50\% \), then the prevalence of DHF was 11/92 (12%). The clinical characteristics of these patients with DHF versus patients with reduced LVEF are shown in Table 6. The mean age and the systolic blood pressure of patients with DHF were significantly higher as compared to patients with reduced LVEF. In addition, the echocardiographic measurements of LV wall thickness (intraventricular septum and posterior wall thickness) were significantly higher in patients with DHF as compared to patients with reduced LVEF. Although, the proportion of patients who were female or who had a previous history of hypertension was much higher in patients with DHF as compared to

<table>
<thead>
<tr>
<th>Variables</th>
<th>Ratio</th>
<th>95% confidence interval</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages(^a) (years)</td>
<td>1.46</td>
<td>(1.26, 1.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>0.83</td>
<td>(0.52, 1.33)</td>
<td>0.44</td>
</tr>
<tr>
<td>History of IHD/MI</td>
<td>1.21</td>
<td>(0.67, 2.19)</td>
<td>0.52</td>
</tr>
<tr>
<td>Abnormal ECG</td>
<td>0.77</td>
<td>(0.48, 1.22)</td>
<td>0.26</td>
</tr>
<tr>
<td>LVEF(^a) (%)</td>
<td>0.82</td>
<td>(0.55, 1.21)</td>
<td>0.3</td>
</tr>
<tr>
<td>Left atrium (cm)</td>
<td>1.93</td>
<td>(1.32, 2.71)</td>
<td>0.001</td>
</tr>
<tr>
<td>LAVI(^b) (ml/m(^2))</td>
<td>4.21</td>
<td>(2.50, 7.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E wave (cm/s)</td>
<td>0.93</td>
<td>(0.31, 2.87)</td>
<td>0.92</td>
</tr>
<tr>
<td>A wave (cm/s)</td>
<td>4.83</td>
<td>(1.97, 11.86)</td>
<td>0.001</td>
</tr>
<tr>
<td>E/A</td>
<td>0.67</td>
<td>(0.43, 1.03)</td>
<td>0.07</td>
</tr>
<tr>
<td>PW thickness (cm)</td>
<td>2.35</td>
<td>(0.79, 6.97)</td>
<td>0.12</td>
</tr>
<tr>
<td>IVS thickness (cm)</td>
<td>3.58</td>
<td>(1.51, 8.47)</td>
<td>0.004</td>
</tr>
<tr>
<td>DT(^c) (ms)</td>
<td>0.91</td>
<td>(0.62, 1.34)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

LVEF=left ventricular ejection fraction, LAVI=left atrium volume index, DT=deceleration time, IHD=ischemic heart disease, IVS=interventricular septum, PW=posterior wall, MI=myocardial infarction.

\(^a\) Ratios given for a 10-unit increase in the explanatory variable.
\(^b\) Explanatory variable analysed on the natural log scale.
\(^c\) Ratios given for a 100-unit increase in the explanatory variable.

\( \text{LVEF} \geq 50\% \)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Ratio</th>
<th>95% confidence interval</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(^a) (years)</td>
<td>1.28</td>
<td>(1.09, 1.51)</td>
<td>0.003</td>
</tr>
<tr>
<td>LAVI(^b)</td>
<td>2.81</td>
<td>(1.60, 4.92)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\(^a\) Ratios given for a 10-unit increase in the explanatory variable.
\(^b\) Explanatory variable analysed on the natural log scale.

\( \text{LVEF} \geq 50\% \)
Fig. 2. The area under the receiver operating characteristic (ROC) curve for NTproBNP for the detection of elevated LAVI in patients with LVEF $\geq 50\%$ (A) and in patients with and without LVEF $\geq 50\%$ (B).
patients with reduced LVEF, these parameters failed to achieve statistical significance.

5. Discussion

This is the first prospective study to demonstrate that LAVI is an independent predictor of serum NTproBNP, in patients with a suspected history of HF and a normal LVEF (DHF). Thus in the absence of significant mitral valve disease or atrial fibrillation, an elevated LAVI is a reliable marker for diagnosis of HF in patients with suspected history of HF but preserved LVEF. Our univariate analysis demonstrates that age and traditional echocardiographic parameters including LA dimension, LAVI, peak transmural A velocity and interventricular septum thickness are significantly predictive of serum NTproBNP in these patients. However, multivariate analysis indicates that LAVI is the most powerful independent predictor of serum NTproBNP even after adjustment for confounding covariates such as age. Consistent with other studies in the literature, in patients with heart failure with a normal LVEF, traditional transmitral Doppler inflow parameters correlated poorly with NTproBNP. Conversely, correlates of DD such as age, LV wall thickness, LV mass index, diabetes mellitus and deceleration time of E wave are all predictors of LAVI. As would be expected of those with isolated DHF, in comparison with the group of patients with an LVEF <50%, the group with an increased LAVI and a normal LVEF appear to have a higher prevalence of elderly patients, females, history of systemic hypertension, and increased LV thickness. Thus, this study suggests that LAVI may serve as a useful marker for diastolic heart failure.

Abnormalities in diastolic function are increasingly recognised to contribute to the signs and symptoms as well as to the prognosis of heart failure [11], and are often grossly independent of systolic ventricular function (subtle systolic abnormalities may be discernable [30]). The complex pathophysiological determinants have rendered diastolic function arduous to assess using simple and reproducible tools such as Doppler mitral inflow echocardiography. However, a combination of Doppler mitral inflow assessment and TDI has been recently shown to be predictive of high left ventricular filling pressure even in the presence of normal LVEF [18,19]. None of these studies were performed in a population with symptoms and signs suggestive of heart failure. Hence, the value of TDI in such a population remains unknown.

An extensive literature attests to the value of LAVI in both haemodynamic [23] and prognostic assessment in a variety of settings [20,21,31–35]. Indeed a number of investigators have even demonstrated the utility of LAVI in predicting cardiovascular outcomes in an unselected community screening programme [20,28]. These observations coupled with recent studies suggesting that LA volume change rate (d[LAVI]/dt) during diastole is useful in evaluating DD [36] provide a rationale supporting our observations relating LAVI and DD. The putative mechanism for this association may relate directly to the role of increased LV filling pressures acting through an open mitral valve orifice, affecting an increased wall tension and as a consequence of Laplace’s law causing left atrial distension. However, while chronically raised high LV filling pressures will significantly

Table 4
Univariate regression analysis of clinical and echocardiographical variables to predict LAVI in patients with LVEF ≥50%

<table>
<thead>
<tr>
<th>Variables</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>2.11</td>
<td>(1.14, 3.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>0.84</td>
<td>(−2.18, 3.89)</td>
<td>0.58</td>
</tr>
<tr>
<td>History of IHD/MI</td>
<td>2.54</td>
<td>(−1.25, 6.33)</td>
<td>0.19</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.92</td>
<td>(−1.15, 5.00)</td>
<td>0.22</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.83</td>
<td>(−1.05, 6.71)</td>
<td>0.15</td>
</tr>
<tr>
<td>Abnormal ECG</td>
<td>1.65</td>
<td>(−1.32, 4.61)</td>
<td>0.27</td>
</tr>
<tr>
<td>Pulse (beats/min)</td>
<td>−1.27</td>
<td>(−2.44, −0.09)</td>
<td>0.04</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>−0.18</td>
<td>(−0.95, 0.60)</td>
<td>0.64</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>0.22</td>
<td>(−0.79, 1.23)</td>
<td>0.67</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>−0.18</td>
<td>(−0.84, 0.50)</td>
<td>0.61</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>−0.16</td>
<td>(−0.44, 0.13)</td>
<td>0.27</td>
</tr>
<tr>
<td>LV diastolic dimension (cm)</td>
<td>0.54</td>
<td>(−1.16, 2.85)</td>
<td>0.64</td>
</tr>
<tr>
<td>LV systolic dimension (cm)</td>
<td>1.33</td>
<td>(−1.50, 4.16)</td>
<td>0.35</td>
</tr>
<tr>
<td>IVS thickness (cm)</td>
<td>12.2</td>
<td>(7.00, 17.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PW thickness (cm)</td>
<td>14.6</td>
<td>(8.08, 21.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV Mass Indexa (g/m²)</td>
<td>0.97</td>
<td>(0.59, 1.34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E wave velocity (cm/s)</td>
<td>0.36</td>
<td>(−0.37, 1.10)</td>
<td>0.33</td>
</tr>
<tr>
<td>A wave velocity (cm/s)</td>
<td>0.50</td>
<td>(−0.11, 1.11)</td>
<td>0.10</td>
</tr>
<tr>
<td>Ea (cm/s)</td>
<td>−0.52</td>
<td>(−4.24, 3.18)</td>
<td>0.79</td>
</tr>
<tr>
<td>Deceleration timea (ms)</td>
<td>−0.24</td>
<td>(−0.49, 0.02)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

a Coefficients given for a 10-unit increase in explanatory variable.

Table 5
Multivariate regression analysis of each variables to predict LAVI in patients with LVEF ≥50%

<table>
<thead>
<tr>
<th>Variables</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agea (years)</td>
<td>2.03</td>
<td>(1.03, 3.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3.39</td>
<td>(−0.28, 7.07)</td>
<td>0.07</td>
</tr>
<tr>
<td>PW thickness (cm)</td>
<td>10.2</td>
<td>(3.56, 16.84)</td>
<td>0.003</td>
</tr>
<tr>
<td>Deceleration time (ms)</td>
<td>−0.25</td>
<td>(−0.45, −0.05)</td>
<td>0.02</td>
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</tbody>
</table>

a Coefficients given for a 10-unit increase in explanatory variable.

Table 6
Clinical and echocardiographic variables in patients with diastolic heart failure and systolic heart failure (LVEF<50%)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Diastolic heart failure (n=11)</th>
<th>Systolic heart failure (n=24)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>80 ± 6</td>
<td>74 ± 9</td>
<td>0.03</td>
</tr>
<tr>
<td>Sex: female (%)</td>
<td>73</td>
<td>60</td>
<td>0.11</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>146 ± 17</td>
<td>130 ± 17</td>
<td>0.02</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>80 ± 9</td>
<td>78 ± 26</td>
<td>0.75</td>
</tr>
<tr>
<td>NTproBNP (pmol/l)</td>
<td>49 ± 34</td>
<td>344 ± 599</td>
<td>0.1</td>
</tr>
<tr>
<td>IVS thickness (cm)</td>
<td>1.4 ± 0.3</td>
<td>1.0 ± 0.24</td>
<td>0.005</td>
</tr>
<tr>
<td>PW thickness (cm)</td>
<td>1.2 ± 0.17</td>
<td>0.98 ± 0.22</td>
<td>0.005</td>
</tr>
<tr>
<td>MI/HHD (%)</td>
<td>27</td>
<td>46</td>
<td>0.5</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>73</td>
<td>33</td>
<td>0.07</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>18</td>
<td>33</td>
<td>0.6</td>
</tr>
</tbody>
</table>
raise LAVI, milder forms of DD are unlikely to do so [20].
Our study confirms this probable underestimation; despite
a mean age of >69 years and a preponderance of women
in our study; the prevalence of isolated DD was only
12.0%; a third of expected from published community
studies. While this may simply reflect a chance statistical
error, it is likely that LAVI is insensitive to milder forms of
DD. Although it may pragmatically be suggested that the
clinical consequences of mild DD are insignificant com-
pared to those in severe DD, this speculation must await
formal studies; mild DD in the context of our population
may indeed prove prognostically significant. However, we
postulate that in patients with symptoms and signs
suggestive of heart failure with preserved LVEF, a normal
LAVI may make the diagnosis of heart failure unlikely.

The converse may also be true; while the role of mitral
regurgitation (MR) in causing LA distension is well
recognised, hence the exclusion of patients with MR at
baseline in this study; especially in the context of ischemia,
dynamic changes in MR are increasingly recognised [37];
this may not be evident at the time of the LAVI assessment
but may nevertheless chronically contribute to LA disten-
tion. Furthermore, other hitherto unknown causes of
intrinsic LA remodelling in the absence of raised filling
pressures may exist. These and other influences would raise
LAVI and lead to an overestimation of DD.

Even our standard, NTproBNP, may be imperfect. While
studies in high-risk patients have clearly established the
sensitivity of this neurohormone in assessing DD [25,38–
40], other studies probably encompassing patients with
lower grades of DD demonstrate a reduced sensitivity [41].
Overestimation of NTproBNP may also occur; a number of
conditions such as coronary disease, obesity, pulmonary
disease and renal failure increase NTproBNP levels. Indeed
the reference range for NTproBNP is also highly population
dependant. Similar to other techniques employed to assess
DD, it is likely that in those with milder forms of DD, even
NTproBNP may prove inadequate. Nevertheless, the AUC
of our ROC curve would suggest that NTproBNP sensi-
tively identifies LAVI and DD in this and therefore similar
populations. Indeed, a population study found natriuretic
peptide to be an independent marker of mortality in patients
with heart failure and preserved LVEF [42].

6. Study limitations

The present study is relatively small and uses a select
referral-based albeit prospective population; this may limit
the statistical power and general applicability of our study.
Furthermore, the use of apical imaging and geometric
assumptions about the conversion of 2D atrial parameters to
LAVI may ultimately represent sources of error; these are
however well validated and standardised techniques that are
generally used in the assessment of LAVI. TDI is a new
modality for the assessment of LV diastolic function.

However, we have not incorporated TDI in this study.
Furthermore, the lack of gold standards for the diagnosis of
heart failure with preserved LVEF had impacted on the
selection of patients. In this study, we had adopted a clinical
approach accepting signs and symptoms of heart failure as a
requirement.

7. Conclusions

Our study suggests that increased LAVI, in the absence
of mitral value disease or atrial flutter or fibrillation, is a
reliable indicator of heart failure in the presence of normal
LVEF. This simple parameter may be used to rule out heart
failure in patients with normal LVEF.

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