A new method for quantification of left ventricular systolic function using a corrected ejection fraction

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Aims

Left ventricular ejection fraction (EF) is a suboptimal measure of ventricular function. Recent mathematical modelling of left ventricular contraction has shown that the EF is determined by both myocardial shortening (strain) and by end-diastolic wall thickness. Increasing end-diastolic wall thickness resulted in augmented radial wall thickening. This may result in a significant ‘overestimation’ of ventricular systolic function as assessed by the EF. This study proposes a new measure of ventricular systolic function, the corrected EF (EFc) to allow for the presence of concentric left ventricular hypertrophy (LVH).

Methods and results

The study uses a new two-layer, three-dimensional mathematical model of ventricular contraction. Changes in end-diastolic wall thickness in addition to long-axis and mid-wall circumferential strain were modelled. Iso-strain lines were obtained where myocardial shortening (strain) is constant; EF increases with increasing end-diastolic wall thickness. The corrected EF is determined by following the iso-strain lines to the equivalent EF in the absence of hypertrophy (e.g. 9 mm thickness). For example, an individual with a mean end-diastolic wall thickness of 20 mm and measured EF of 60% has a corrected EF (EFc) of 37%.

Conclusion

The study shows that the EF is determined by absolute wall thickening and provides a nomogram for comparing EF when LVH is present. The EFc is a potential new measure of left ventricular systolic function. Its possible role will need validating in mortality trials.

Methods

The study uses a new two-layer, three-dimensional mathematical model of ventricular contraction. Changes in end-diastolic wall thickness in addition to long-axis and mid-wall circumferential strain were modelled. Iso-strain lines were obtained where myocardial shortening (strain) is constant; EF increases with increasing end-diastolic wall thickness. The corrected EF is determined by following the iso-strain lines to the equivalent EF in the absence of hypertrophy (e.g. 9 mm thickness). For example, an individual with a mean end-diastolic wall thickness of 20 mm and measured EF of 60% has a corrected EF (EFc) of 37%.

Keywords

Heart failure • Stroke volume • Ejection fraction • Strain • Left ventricular systolic function

Introduction

Heart failure (HF) patients have unimodal distribution of left ventricular ejection fraction (EF).1 Heart failure is usually divided into two types, heart failure with a reduced EF (HFREF) and heart failure with a preserved EF (HFPEF). Concentric left ventricular hypertrophy (LVH) and a relatively normal end-diastolic volume are common in the latter.2

Studies have shown that prognosis in HF worsens as the EF decreases.3–5 However, EF is regarded as a suboptimal measure of ventricular systolic function with a limited role in assessing prognosis5 and in the assessment for the need of a cardiac transplant.7 Nor does the EF correlate with either functional capacity or maximal myocardial oxygen consumption in HF.8,9 The EF is unhelpful in assessing prognosis with a measure above 45%3 and in patients admitted with HFPEF.10,11 Furthermore, the presence of LVH alone is an important risk factor independent of the EF.12,13 Nevertheless, EF is widely used, with a wealth of data including its use in deciding the appropriateness of valve surgery, pharmacological treatment, and device therapy.14,15

Alternative measures of systolic function such as mitral annular displacement,16–18 tissue Doppler velocities,19 and longitudinal strain20–22 may provide superior measures of ventricular systolic function and prognosis. It has been assumed that a decline in longitudinal strain is accompanied by a compensatory increase in circumferential or radial function to maintain the EF in HFPEF.23 In non-hypertensive diabetics without LVH, the radial strain was increased, whereas the longitudinal strain was reduced.24

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In asymptomatic mildly hypertensive individuals, radial strain was increased; however, the radial strain declined as symptoms developed, hypertrophy progressed, and the severity of HF increased.25

In more advanced disease, where there is concentric LVH and a normal EF, it is increasingly apparent that not only is the longitudinal strain reduced but also both circumferential and radial strain are decreased (see Table 1).26 Similar abnormalities occur in other hypertrophic conditions such as aortic stenosis,27 hypertension,27 amyloidosis,28 hypertrophic cardiomyopathy,29 and HFPEF (see Table 1).30–32 These findings suggest that widespread (i.e. global) reduction in strain in pathological LVH is common despite a normal EF.

There is a strong drive to improve on current methods of assessment of left ventricular systolic function and prognosis. This study addresses the apparent discrepancy in the EF and the myocardial strain by proposing an adjustment of the EF, the corrected EF (EFc), to allow for the presence of concentric LVH.

**Methods**

To measure the independent effects of changes in end-diastolic wall thickness and myocardial strain, a new method was developed from a previously described model.33,34 The current paper employs the geometric model based on the cylindrical–hemispherical shape35 using the formula $V = \pi (W/2)^2$, where $V$ is the internal volume, $W$ is the inner wall thickness, and $H$ is the length of the long axis. The model uses a new two-layer approach whereby the myocardium is assumed to be a non-compressible elastomer. The internal end-systolic volume was calculated by subtracting the total muscle volume (MV) from the external end-systolic volume. The stroke volume and the EF, etc. were calculated in the usual manner. The middle layer is the site of the circumferential fibres with longitudinal fibres present in the sub-endocardial (inner shell) and sub-epicardial (outer shell) layers.36 This model allows both the longitudinal shortening and the mid-wall circumferential strain to be adjusted independently. Variables adjusted were end-diastolic wall thickness from normal (0.9 cm) to hypertrophic (2.1 cm) and strain.

Strain is defined as myocardial deformation and is expressed as a percentage shortening, i.e. Cauchy strain, $e = 100\% \left( L_n - L_0 \right) / L_0$%, where $L_n$ is the original length and $L_0$ is the new length. Circumferential strain is the % shortening derived from $2\pi r$, i.e. $W/2\pi$ of the mid-wall and longitudinal strain from long-axis length $L$ in systole and diastole where strain = $Ld - Ls/Ld$ (see Figure 1). Circumferential strain was adjusted as follows: normal (−19%), mildly reduced (−14%),

**Table 1**

<table>
<thead>
<tr>
<th>Group</th>
<th>Longitudinal strain (%)</th>
<th>Circumferential strain (%)</th>
<th>Radial strain (%)</th>
<th>LVEF (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Patient</td>
<td>Control</td>
<td>Patient</td>
<td>Control</td>
</tr>
<tr>
<td>Concentric LVH</td>
<td>22.9</td>
<td>−17.9**</td>
<td>23.7</td>
<td>−20.4**</td>
<td>+74.4</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>20.3</td>
<td>−14.6**</td>
<td>19.5</td>
<td>−15.2**</td>
<td>+38.9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20.3</td>
<td>−17.2**</td>
<td>19.5</td>
<td>−17.0**</td>
<td>+38.9</td>
</tr>
<tr>
<td>HCM</td>
<td>20.3</td>
<td>−15.1**</td>
<td>19.6</td>
<td>−16.8**</td>
<td>+36.8</td>
</tr>
<tr>
<td>HFPEF</td>
<td>19.0</td>
<td>−12.0*</td>
<td>20.0</td>
<td>−15.0**</td>
<td>+47.0</td>
</tr>
<tr>
<td>HFPEF</td>
<td>20.9</td>
<td>−18.9*</td>
<td>na</td>
<td>na</td>
<td>+49.2</td>
</tr>
<tr>
<td>HFREF</td>
<td>21.0</td>
<td>−16.0**</td>
<td>26.4</td>
<td>−20.7**</td>
<td>+44.3</td>
</tr>
<tr>
<td>HFREF</td>
<td>19.0</td>
<td>−4.0*</td>
<td>20.0</td>
<td>−7.0**</td>
<td>+47.0</td>
</tr>
</tbody>
</table>

The table shows observational data including resting peak systolic strain. Note there is a reduction in longitudinal strain associated with a similar reduction in circumferential and radial strain when left ventricular hypertrophy is present. Abnormalities of strain are more marked when EF is reduced.

na, data not available; ns, P-value > 0.05; *P < 0.01; **P < 0.001; LVH, left ventricular hypertrophy; HCM, hypertrophic cardiomyopathy.

**Figure 1** Geometric shape used in modelling technique: see Methods section for details.
moderately reduced (−9.0%), and severely reduced (−6.0%). Longitudinal ($e_L$) and mid-wall circumferential ($e_M$) myocardial strain appear to be related in a curvilinear manner (using the quadratic equation $e_L = 0.0294 e_M^2 + 0.361 e_M$) derived from data by Wang et al.\textsuperscript{30}. Longitudinal strain was determined from this relationship.

Other parameters such as external end-diastolic long-axis length were kept constant. The end-diastolic volume was adjusted to normalize stroke volume to mimic the findings in chronic HF.\textsuperscript{37–40} It is also assumed that heart rate, body habitus, valvular regurgitation, and all other physiological variables are identical in all individuals.

Results

Using the new more complex model allowed adjustment of longitudinal and circumferential strain independently. The modelling shows a curvilinear relationship between the EF, end-diastolic wall thickness, and myocardial strain (Figure 2). This provides a potential nomogram for comparing EFs in individuals with increasing wall thickness but similar strain values.

Absolute wall thickening is determined by both relative wall thickening (i.e. strain) and end-diastolic wall thickness (Figure 3). However, EF is most closely related to absolute wall thickening (Figure 4). The model also predicts a reciprocal relationship between end-diastolic volume and EF (Figure 5A). The complex relationship between longitudinal strain and EF is shown in Figure 6A.

Discussion

This study uses mathematical modelling to assess the effects of peak systolic wall strain and end-diastolic wall thickness on EF. The EF of an individual with LVH can be compared with the equivalent EF without hypertrophy given the same overall strain. This is achieved by comparing their relative positions with respect to the iso-strain lines shown in Figure 2. For example, an individual with an EF of 60% and a mean end-diastolic wall thickness of 20 mm would have the same strain values as an individual with an EF of 37% and a normal end-diastolic wall thickness.

The modelling also suggests a near linear relationship between absolute left ventricular wall thickening and EF; this suggests that EF is determined predominantly by absolute wall thickening rather than relative wall thickening or strain (Figures 3 and 4). This study explains the apparent paradox of reduced longitudinal,
circumferential, and radial strain, and yet a normal EF in concentric LVH. The increased end-diastolic wall thickness results in an increase in absolute radial thickening. Specifically, although the relative radial thickening (radial strain) may be reduced, the absolute radial thickening may still be relatively normal. The external dimensions of the left ventricle remain relatively normal during contraction and, therefore, if absolute radial thickening is normal, endocardial displacement and EF are also normal. In effect, a normal EF can occur in the setting of reduced contractile function (global strain) and concentric LVH.

**Relevance to clinical practice**

The findings of this study could relatively easily be incorporated into standard imaging equipment such as echocardiography.
cardiac magnetic resonance imaging, or computerized tomography. For example, from a simple M-mode echocardiographic slice from the parasternal view the EF could be determined by the Teichholtz method or similar, and the mean end-diastolic wall thickness determined (from the antero-septum and posterior walls). The EFc could then be calculated automatically. Alternatively, a table could be produced to find the EFc. More sophisticated algorithms could be derived for three-dimensional volumetric analysis from echocardiographic, etc. imaging.

This method may have a number of advantages over using conventional methods for measuring the myocardial strain. For example, measuring the EF is often easier, particularly using contrast for left ventricular opacification. It is also quicker than using myocardial strain requiring no off-line analysis and may even be more accurate, particularly where the imaging is suboptimal and speckle tracking may be unreliable. Different echocardiographic equipment use dissimilar algorithms to derive strain values and therefore it is uncertain whether values from one manufacturer or model will correlate with other machines. The EFc is independent of the measured strain and may therefore provide more comparable data. Most strain studies assess the peak systolic strain rather than the maximum strain at end-systole. When dysynchrony is present, the peak systolic strain will differ from the timing of the minimum end-systolic volume. This would lead to

Figure 5 Predicted reciprocal relationship between end-diastolic volume and ejection fraction. (A) This graph shows the predicted relationship between end-diastolic volume and ejection fraction. Note how with increasing wall thickness the data point is shifted to the left and upward, increasing ejection fraction; decreasing strain (less negative) results in a shift downward and to the right. (B) This data predicted by the modelling compares favourably with actual observational clinical data from Gaasch et al. © 2008 (Permission received from Elsevier copyright © 2008)
an overestimate of the effective strain and may be a limitation of strain studies. The EFc would compensate for the ‘incorrect’ strain value and may prove more accurate than peak strain values in assessing the prognosis.

Limitations

The study was based on theoretical mathematical modelling and an idealized left ventricular shape. The role of EFc will need to be confirmed by studies assessing prognosis to see if it improves other currently available methods of assessing left ventricular systolic function. Its role in asymmetric hypertrophy and in the presence of regional wall motion abnormalities may also require further evaluation. The method may be supported by applying the data to mortality trials already performed or prospectively in future studies.

Standard body habitus was assumed and therefore the nomogram may not be applicable to extremes in size and children. However, EF reference ranges are the same independent of body size, gender, etc. Any adjustments for size may be achieved by choosing a different ‘normal’ end-diastolic wall thickness. Furthermore, other parameters such as heart rate and presence of valvular regurgitation may influence both EF and EFc. The close matching of the mathematical model’s prediction and clinical observational trials (see Figures 5B and 6B) would suggest that the assumptions are accurate for most individuals. Future studies are required to confirm that the degree of concentric hypertrophy and strain abnormalities explains the distribution of EF and prognosis in HF.

Summary

The EFc provides a potential new measure of left ventricular systolic function which would be simple to obtain. In effect, it indirectly measures myocardial strain and adjusts for the presence of LVH. It might provide additional prognostic information complementary to, or easier and more reliable than, measuring global strain, etc. Its possible role will need verification with trials examining the prognosis in individuals with concentric LVH or HF.

Conflict of interest: none declared.

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35. Maciver DH. Is remodeling the dominant compensatory mechanism in both chronic heart failure with preserved and reduced left ventricular ejection fraction? Basic Res Cardiol 2010;105:227–34.


