Short-axis epicardial volume change is a measure of cardiac left ventricular short-axis function which is independent of myocardial wall thickness.

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Running title: Wall thickness-independent short-axis function

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Abstract

BACKGROUND Fractional shortening (FS) by echocardiography is considered to represent the short-axis contribution to the stroke volume (SV), also called short-axis function. However, FS is mathematically coupled to the amount of myocardium, since it rearranges during atrioventricular plane displacement (AVPD). The SV is the sum of the volumes generated by 1) reduction in outer volume of the heart, and 2) inner AVPD. The long-axis contribution to the SV is generated by AVPD, and thus the short-axis contribution is the remaining outer volume change of the heart, which should be unrelated to myocardial wall thickness. We hypothesized that both endocardial and midwall shortening indexed to SV are dependent on myocardial wall thickness, whereas epicardial volume change (EVC) indexed to SV is not. METHOD Twelve normals, 12 athletes and 12 patients with dilated cardiomyopathy (ejection fraction<30%) underwent cine cardiac magnetic resonance imaging. Left ventricular long-axis function was measured as the portion of the stroke volume, in ml, generated by AVPD. EVC was defined as SV minus long-axis function. Endocardial and midwall shortening were measured in a midventricular short-axis slice. RESULTS Endocardial shortening/SV and midwall shortening/SV both varied in relation to end-diastolic myocardial wall thickness (R²=0.16, p=0.008 and R²=0.14, p=0.012, respectively) whereas EVC/SV did not (R²=0.00, p=0.37). CONCLUSIONS FS is dependent on myocardial wall thickness while EVC is not and therefore represents true short-axis function. This is not surprising considering that FS is mainly caused by rearrangement of myocardium secondary to long-axis function. FS is therefore not synonymous with short-axis function.
Background

The end product of cardiac pumping is the volume of blood ejected during one cardiac cycle; the stroke volume. The stroke volume can be seen as the sum of two parts, namely the volume of blood generated by long-axis function and the volume of blood generated by short-axis function. We have previously shown that 1) long-axis function corresponds to the volume of blood generated by atrioventricular plane displacement (AVPD), 2) short-axis function corresponds to the volume of blood generated by the epicardial volume change (EVC) of the heart, and 3) the sum of these two volumes equals the stroke volume (5, 6). Using these definitions, the normal heart has been shown to have a left ventricular stroke volume which is generated by 60% long-axis function and 40% short-axis function, whereas the right ventricular stroke volume is generated by 80% long-axis function and 20% short-axis function (5).

In echocardiography, long-axis function has been quantified in long-axis images as the movement of the atrioventricular plane during systole, also called AVPD (9). By analogy, short-axis function has been quantified as fractional shortening (FS) and measured as the decrease in endocardial diameter in the short-axis plane (10, 15). Moreover, endocardial FS has been found to be influenced by myocardial hypertrophy, and thus midwall FS has been proposed as a measure of short-axis function which is less influenced by myocardial hypertrophy (2, 7). The measures involved in calculating both endocardial and midwall shortening and fractional shortening, as well as the EVC are illustrated in Figure 1. Importantly, absolute shortening or fractional shortening employing measurement of the endocardial or midmural inner diameter of the left ventricle are currently used to
assess short-axis function during both systole (13, 17, 20) and diastole (14), and to compare the relationship between long- and short-axis function (1, 3, 4, 16, 19).

However, both endocardial and midmural FS are measures which are mathematically coupled to long-axis function through rearrangement of myocardium which occurs when the atrioventricular plane moves towards the apex during systole. Thus, both endocardial and midmural FS appear to be measures of short-axis function which also are influenced by the amount of myocardium, see Figure 2. Yet, short-axis function can be measured as EVC which, theoretically, is not influenced by the amount of myocardium.

We hypothesized that both endocardial and midwall shortening are dependent on myocardial wall thickness, whereas the short-axis EVC is not. The current study sought to address this hypothesis by measuring both left ventricular endocardial and midmural shortening as well as EVC, and analyzing how these measures relate to myocardial wall thickness measured by cardiovascular magnetic resonance (CMR) imaging. Furthermore, we sought to assess the relationship between long- and short-axis function by CMR.
Methods

Study population

The study was approved by the local ethics committee. Normals and athletes provided written informed consent and the local ethics committee provided a waiver of written informed consent for retrospective inclusion of patients. We studied 12 healthy volunteers, 12 Swedish national elite triathletes and 12 patients with dilated cardiomyopathy (ejection fraction<30%). This population has been studied previously (6).

CMR imaging

All subjects underwent CMR imaging in the supine position. Imaging was undertaken with a 1.5T scanner (Intera, Philips, Best, the Netherlands) using a five element cardiac synergy coil and a cine steady state free precession sequence as previously described (6). Cine image acquisition included a contiguous short-axis stack, and also the two-chamber, four-chamber and left ventricular outflow tract long-axis views. In short, spatial resolution was typically 1.4 x 1.4 x 8 mm and temporal resolution 30 ms per image.

Image analysis

Left ventricular stroke volume was determined by manual planimetry in short-axis slices (11). AVPD was measured as the mean of six measurements, namely, one measurement at each of the two atrioventricular valve plane positions per image in the two-chamber, four-chamber and left ventricular outflow tract long-axis views, as previously described (6). Left ventricular long-axis function (LAF) was measured as the portion of the stroke volume generated by AVPD using the following formula:
where Aepid is the mean of the largest end-diastolic epicardial area of the left ventricle encompassed by the AVPD. For extensive details and volumetric validation of this method, see Carlsson et al (6). Figure 3 summarizes the method for measuring long-axis function. EVC was defined as stroke volume minus long-axis function.

Endocardial and midwall shortening (mm) and fractional shortening (%) were calculated from measurements in a single midventricular short-axis slice as described in Figure 1. The endocardial diameter (Dendo) of the left ventricle was calculated as two times the endocardial radius. The endocardial radius (Rendo) and epicardial radius (Repi) were calculated according to the following formula:

\[
R_{\text{endo}} = \left( \frac{A_{\text{endo}}}{\pi} \right)^{\frac{1}{2}} \quad \text{(Formula 2)}
\]

\[
R_{\text{epi}} = \left( \frac{A_{\text{epi}}}{\pi} \right)^{\frac{1}{2}} \quad \text{(Formula 3)}
\]

where \( A_{\text{endo}} \) and \( A_{\text{epi}} \) are the endocardial and epicardial areas of a midventricular short-axis slice, respectively, and \( \pi \) is 3.14. Endocardial diameter was measured in both end diastole and end systole. Midwall diameter (Dmw) was calculated according to:

\[
D_{\text{mw}} = \frac{1}{2}(WT) + D_{\text{endo}} + \frac{1}{2}(WT) \quad \text{(Formula 4)}
\]

where WT is wall thickness and Dendo is the endocardial diameter. Wall thickness was determined as the difference between epicardial and endocardial radii as determined by Formulas 2 and 3. Midwall diameter was measured in both end diastole and end systole.
Statistical analysis was performed with the software SPSS (version 16). Data are presented as mean ± standard error of the mean (SEM). Differences between subject groups were tested with the Mann-Whitney test. Univariate regression was performed using Pearson’s correlation coefficient and expressed as its square (R²). Differences between linear and logarithmic regression were tested by comparing the mean squared residuals using a paired t-test. P<0.05 was considered statistically significant.
Results

Subject characteristics including measures of left ventricular function are displayed in Table 1. Endocardial and midwall shortening were influenced by wall thickness (p<0.05 for both) while EVC was not (Table 2). The dependence of endocardial shortening on wall thickness is illustrated in Figure 3 which shows representative long- and short-axis MR images of two subjects. The subject with markedly different end-diastolic wall thickness has a greater endocardial shortening.

Figure 5 illustrates the relationship between EVC and long-axis function. There was a significant relationship using both linear (y = 0.53x + 8.5, R^2=0.35, p<0.001) and logarithmic (y = 33.0 ln (x) – 92.8, R^2=0.39, p<0.001) regression. However, the linear and logarithmic regression lines did not differ from each other (p=0.07).
Discussion

The main finding of the current study is that both endocardial and midwall shortening are affected by wall thickness, while EVC is not. This implies that FS is not solely a measure of short-axis function and should not be referred to as such.

It is not known why cardiac physiologists and cardiologists have focused their attention on the endocardium when trying to quantify short-axis function. It may be that the tradition of measuring left ventricular volumes with endocardial delineations in cine cardiac tomographic images has contributed to this endocardial focus. The left ventricular stroke volume is typically measured by delineating the endocardial surface of the left ventricle in end diastole and end systole. However, the volume of left ventricular myocardium is nearly constant during the cardiac cycle (6). Thus, the stroke volume is the same when measured by delineating the endocardial surface as when measured by delineating the epicardial surface of the left ventricle in end diastole and end systole, respectively (6).

This study has presented a theoretical model and empirical evidence showing that endocardial or midwall shortening is by definition influenced by myocardial wall thickness. It is not surprising that both endocardial and midmural FS are related to myocardial wall thickness, since they are mathematically coupled. An appendix based on the work of Riordan and Kovacs (14) is provided which provides the details of this mathematical relationship.

The current work has been based on a previously presented and validated theoretical framework for measurement of the short- and long-axis function as mutually exclusive and complementary volumetric components of the stroke volume (5, 6). Absolute (mm) or relative (%) FS employing measurement of the endocardial...
or midmural inner diameter of the left ventricle have been used to assess short-axis function during both systole (13, 17, 20) and diastole (14). Notably, the current study measured the volume of long- and short-axis contribution to the stroke volume between end diastole and end systole. By analogy, the same methods could be applied to each time frame throughout both systole and diastole. Such future studies might be of value in order to provide further insight into the relative contributions of long- and short-axis function during the E-wave and A-wave of diastolic filling.

We have shown that the epicardial volume change can be visualized as a small change in short-axis epicardial area. This finding confirms that of a previous study which called this phenomenon the “crescent effect” (18). That study performed two-dimensional measurements of this space, and the current study built upon those findings in order to quantify the entire volume of the short-axis contribution to the stroke volume.

Furthermore, we found that the relationship between short-axis function (EVC) and long-axis function is linear. FS has been used in studies of the relationship between long- and short-axis function by echocardiography (3, 16) with conflicting results with regards to the linearity of this relationship. Previous studies have showed a linear relation between AVPD and endocardial FS (1, 4, 19). By comparison, Ballo et al showed a non-linear relation between AVPD and midwall FS (3) and claimed that there is a non-linear relationship between circumferential (short-axis) and longitudinal (long-axis) function. However, the current study has shown that the relationship between EVC and long-axis function is linear over a wide range of values for short- and long-axis function.

Our study showed a trend towards a greater long-axis contribution to the stroke volume in patients compared to controls. This may seem counterintuitive
considering that a number of previous studies have shown that the AVPD is reduced in the diseased heart. The patients in our study did indeed have a reduced AVPD. However, the contribution to the stroke volume made by long-axis function is the product of AVPD and epicardial short-axis area. Our patients had larger epicardial short-axis areas due to left ventricular dilatation, thereby contributing to a larger total long-axis function. This finding illustrates that the relative contribution to the stroke volume by long-axis function may be preserved or even increase despite a reduction in AVPD.

In light of the findings in the current study, it may be motivated to reassess the appropriateness of using endocardial or midwall FS when specifically assessing left ventricular short-axis function in future studies. Midwall FS has been successfully used as a measure for diagnostic quantification of left ventricular function in left ventricular hypertrophy. The current study does not question the use of FS as a quantitative measure of ventricular function as such, it merely clarifies that FS is not synonymous with short-axis function. Since FS is dependent on myocardial wall thickness and thus the apparent thickening which occurs as a result of long-axis function, it might be more appropriate to discuss FS in terms of ventricular function without a specification of its relation to a particular short or long axis, or merely endocardial or midwall shortening.

A study using echocardiography measured left ventricular long-axis function and found that it comprised 82% of the stroke volume. Our previous study using CMR found that roughly 60% of the left ventricular stroke volume was generated by long-axis function. CMR is generally considered to be the most accurate modality for volumetric quantification of left ventricular volumes owing to its ability to image the full left ventricle in three dimensions without restrictions on image angulation.
It may be that the discrepancies between CMR and echocardiography are due to difficulties with using two-dimensional echocardiography to accurately acquire short-axis images perpendicular to the long axis of the left ventricle. Two-dimensional echocardiography will remain the everyday tool for assessment of LV function.

**Limitations**

Clinical echocardiography is undertaken with a higher temporal resolution compared to clinical MR imaging. However, although high temporal resolution is important when quantifying velocities, the temporal resolution of MR for quantifying volumes as in the current study is more than sufficient given that temporal resolution was at most 30 ms. Taken together, it may be that MR is more accurate for quantifying true long-axis and short-axis function.

FS is dependent on myocardial wall thickness while EVC represents true short-axis function and is not dependent on myocardial wall thickness. This is not surprising considering that FS is mainly caused by rearrangement of myocardium secondary to long-axis function, whereas EVC is not. FS is therefore not synonymous with short-axis function. We suggest referring to FS as a measure of ventricular function, without specifying its relation to a particular short or long axis.
Acknowledgements

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References


**Figures**

**Figure 1 - Endocardial shortening, midwall shortening and epicardial volume change.**

Schematic illustration of a short-axis view through the left ventricle showing measures involved in calculating endocardial and midwall shortening and fractional shortening, and epicardial volume change (EVC). The dotted line denotes the epicardial border in end diastole. Top row shows the measures for calculation of endocardial shortening. Dendod denotes the endocardial diameter of the left ventricle in the short-axis view in end diastole. Dendoₕ is the corresponding measure in end systole. Endocardial shortening (mm) was calculated as Dendoₕ - Dendoₕ and endocardial fractional shortening (%) was calculated as (Dendoₕ - Dendoₕ) / Dendoₕ. Bottom row shows the measures for calculation of midwall shortening. Dmwₕ denotes the midwall diameter of the left ventricle in the short-axis view in end diastole. Dmwₕ is the corresponding measure in end systole. Midwall shortening (mm) was calculated as Dmwₕ - Dmwₕ and midwall fractional shortening (%) was calculated as (Dmwₕ - Dmwₕ) / Dmwₕ. Adapted from deSimone et al (7).

**Figure 2 - Schematic illustration of the effects of wall thickness on fractional shortening**

The illustration depicts the long-axis (top) and short-axis (middle) of a theoretical model of a left ventricle with (A) no myocardium and only short-axis epicardial volume change, or three model (B-D) with no short-axis epicardial volume change in the setting of (B) no myocardium and only long-axis function, (C) normal.
myocardium, and (D) hypertrophied myocardium with increased wall thickness.

Solid lines represent the borders of the left ventricle in end diastole and dashed lines end systole. The thin dotted line represents the intersection of the long- and short-axis views. All models have the same stroke volume. In Model A, the stroke volume is generated by only short-axis epicardial volume change but no long-axis function. In models B-D, the stroke volume is generated by only long-axis function by way of the atrioventricular plane displacement (AVPD), but not short-axis function. In models C and D, an unchanged volume of myocardium is rearranged between end diastole and end systole. The addition of myocardium to the model in C and D increases the ejection fraction. Note how fractional shortening is influenced by the wall thickness despite the absence of any short-axis function in models C and D. The short-axis function in the form of an epicardial volume change is illustrated in Figure 4.

**Figure 3 - Schematic illustration of how the long-axis contribution to the stroke volume was measured**

**LEFT:** The epicardial contour of a schematic LV with only long-axis pumping and no short-axis pumping. AVPD = atrioventricular plane displacement. The broken lines indicate the position of the AV-plane in end systole. The long-axis contribution to the stroke volume is shown in grey. **MIDDLE:** The grey region is unchanged in size and indicates the outer diameter (d) multiplied by the AVPD. **RIGHT:** Myocardium is added to the model. Myocardium reduces the inner contour of the ventricle but the volume of the myocardium is constant throughout the cardiac cycle. The myocardium is rearranged as it pulls the AV-plane towards the apex. This illustrates how long-axis function contributes to fractional shortening in the short-axis plane (dotted line) in the absence of any short-axis function. Adapted from
Carlsson et al (6). The short-axis function in the form of an epicardial volume change is illustrated in Figure 4.

**Figure 4 - Representative long- and short-axis MR images of two subjects.**
Long axis, short axis and left ventricular (LV) epicardial borders are shown in end diastole (solid lines) and end systole (dashed lines). The subject with markedly increased end-diastolic wall thickness (right) has a greater endocardial shortening, as illustrated by the horizontal arrows in the short-axis images. EVC denotes the epicardial volume change.

**Figure 5 - The relationship between epicardial volume change (short-axis function) and long-axis function**
The dotted line represents the line of linear regression ($R^2=0.35$, $p<0.001$) and the solid line a logarithmic regression ($R^2=0.39$, $p<0.001$). There was no difference between the linear and logarithmic regression lines ($p=0.07$).

**Figure Appendix 1 – A schematic diagram illustrating a simplified cylinder as the left ventricle**
Inner radius ($r_i$), outer radius ($r_o$) and height ($h$) of the cylinder are shown in end diastole (ed, solid lines) and end systole (es, dotted lines).
### Table 1 - Subject characteristics

<table>
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<th>Measure</th>
<th>Normals</th>
<th>Athletes</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects, n</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Age, yr</td>
<td>24±1</td>
<td>35±1**</td>
<td>54±2**</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>5 (42)</td>
<td>4 (33)</td>
<td>4 (33)</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.94±0.03</td>
<td>1.90±0.03</td>
<td>2.03±0.04</td>
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<tr>
<td>Heart rate, beats/min</td>
<td>63±2</td>
<td>55±1</td>
<td>77±2*</td>
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<tr>
<td>LVEDV, ml</td>
<td>185±10</td>
<td>218±10*</td>
<td>333±27**</td>
</tr>
<tr>
<td>LVESV, ml</td>
<td>69±5</td>
<td>78±7</td>
<td>261±24**</td>
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<tr>
<td>LVEF, %</td>
<td>63±1</td>
<td>65±2</td>
<td>22±2**</td>
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<tr>
<td>Endocardial shortening, mm</td>
<td>11.1±0.4</td>
<td>11.8±0.4</td>
<td>8.1±0.4***</td>
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<tr>
<td>Endocardial fractional shortening, %</td>
<td>68±2</td>
<td>68±3</td>
<td>58±3***</td>
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<tr>
<td>Endocardial shortening indexed to stroke volume (mm/ml SV)</td>
<td>0.098±0.004</td>
<td>0.085±0.003*</td>
<td>0.122±0.011*</td>
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<tr>
<td>Midwall shortening, mm</td>
<td>3.9±0.2</td>
<td>4.2±0.1</td>
<td>1.3±0.2**</td>
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<tr>
<td>Midwall fractional shortening, %</td>
<td>21±1</td>
<td>21±1</td>
<td>16±1***</td>
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<tr>
<td>Midwall shortening indexed to stroke volume (mm/ml SV)</td>
<td>0.034±0.002</td>
<td>0.031±0.001</td>
<td>0.019±0.003***</td>
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<td>Short-axis EVC, ml</td>
<td>47±4</td>
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<td>24±3***</td>
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<td>43±2</td>
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<td>Long-axis function, ml</td>
<td>69±4</td>
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<tr>
<td>Long-axis function, %SV</td>
<td>60±2</td>
<td>57±2</td>
<td>67±4</td>
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</table>

BSA = body surface area, LV=left ventricle, EDV=end diastolic volume, ESV=end systolic volume, EF=ejection fraction, SV=stroke volume, EVC=epicardial volume change. *, ** and *** denote p<0.05, p<0.01 and p<0.001 for comparison with Normals, respectively.

### Table 2 - The correlation of end-diastolic myocardial wall thickness (mm) with different measures

<table>
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<th>Measure</th>
<th>R²</th>
<th>p</th>
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<tr>
<td>Endocardial shortening indexed to stroke volume (mm/ml SV)</td>
<td>0.16</td>
<td>0.008</td>
</tr>
<tr>
<td>Midwall shortening indexed to stroke volume (mm/ml SV)</td>
<td>0.14</td>
<td>0.012</td>
</tr>
<tr>
<td>Short-axis epicardial volume change indexed to stroke volume (%SV)</td>
<td>0.00</td>
<td>0.372</td>
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</table>
The purpose of this appendix is to provide a mathematical explanation regarding the theoretical possibility for the influence of wall thickness upon epicardial volume change (EVC), endocardial fraction shortening and midmural fractional shortening.

The left ventricle in end diastole can be approximated as a cylinder (14) with a height in end diastole, $h_{ed}$, an outer radius in end diastole, $r_{oed}$, and an inner radius in end diastole, $r_{ied}$.

The same left ventricle in end systole (dotted lines) can be approximated by a cylinder with a height in end systole, $h_{es}$, an outer radius in end systole, $r_{oes}$, and an inner radius in end systole, $r_{ies}$. See Figure Appendix 1.

The wall thickness in end diastole is proportional to left ventricular mass. The wall thickness, WT, is calculated as follows.

$$WT = r_{oed} - r_{ied}$$

Wall thickness is thereby dependent upon both the outer, epicardial, and the inner, endocardial dimensions of the ventricle.

Also note that the amount of myocardium is unchanged throughout the cardiac cycle. Thus, the myocardium is thicker in end systole compared to end diastole.
The epicardial volume change, ECV, is calculated as follows:

\[ \text{EVC} = (\pi \cdot r_{\text{ed}}^2 \cdot h_{\text{es}}) - (\pi \cdot r_{\text{es}}^2 \cdot h_{\text{es}}) \]

Note that the inner radius of the cylinder, \( r_i \), and thereby the wall thickness, is not involved in this calculation.

By comparison, the endocardial fractional shortening, \( F_{\text{endo}} \), is calculated as follows:

\[ F_{\text{endo}} = \frac{(2 \cdot r_{\text{ed}}) - (2 \cdot r_{\text{es}})}{(2 \cdot r_{\text{ed}})} \]

Also, the midwall fractional shortening, \( F_{\text{mw}} \), is calculated as follows:

\[ F_{\text{mw}} = \frac{(2 \cdot (r_{\text{ed}} + \frac{1}{2} (r_{\text{es}} - r_{\text{ed}}))) - (2 \cdot (r_{\text{es}} + \frac{1}{2} (r_{\text{es}} - r_{\text{es}})))}{(2 \cdot (r_{\text{ed}} + \frac{1}{2} (r_{\text{es}} - r_{\text{ed}}))} \]

Note that calculations of both endocardial and midwall fractional shortening include the inner radius, an endocardial measurement, and are thereby mathematically coupled to wall thickness.

In summary, these formulas show that both endocardial and midwall fractional shortening are functions of the myocardial wall thickness, whereas epicardial volume change is independent of wall thickness.
End diastole

Endocardial shortening

$Dendo_d$

Midwall shortening

$Dmw_d$

End systole

$Dendo_s$

$Dmw_s$

EVC
Stroke volume = Stroke volume = Stroke volume = Stroke volume
AVPD < AVPD < AVPD < AVPD
Ejection fraction = Ejection fraction < Ejection fraction < Ejection fraction
Wall thickness = Wall thickness < Wall thickness < Wall thickness
Fractional shortening > Fractional shortening < Fractional shortening < Fractional shortening
Wall thickness < Wall thickness