Longitudinal myocardial dysfunction in healthy older subjects as a manifestation of cardiac ageing

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Abstract

Background: abnormalities of longitudinal left ventricular (LV) contraction and relaxation may be early markers of cardiac disease. This study was designed to assess the relationship between long-axis LV function and age in healthy subjects.

Methods: 118 healthy individuals aged 57 ± 19 years (range 20–90 years) with no evidence of cardiovascular disease underwent echocardiography with Doppler examination of transmitral flow. To assess longitudinal LV function, systolic (Sm), early diastolic (Em) and late diastolic (Am) mitral annular velocities were measured using colour-coded tissue Doppler imaging.

Results: the left atrium was enlarged (P<0.001) in subjects ≥60 years of age compared to those <60 years, but there were no differences in LV volumetric indices and ejection fraction. Peak E velocity was lower (P<0.001) and peak A velocity of transmitral flow was higher in older subjects (P<0.001) with a higher E/A ratio (P<0.001) and longer isovolumic relaxation time (P=0.001) indicative of impaired ventricular relaxation. Sm and Em mitral annular velocities decreased (P<0.001) and Am velocity increased (P=0.002) in the older group. Em velocity and Em/Am ratio showed a strong negative correlation with age (r =−0.80, P<0.001 and r =−0.78, P<0.001, respectively).

Conclusions: global LV systolic function is preserved but the velocity of long-axis systolic shortening is depressed in older individuals, indicating selective impairment of the longitudinal component of systolic contraction. The decline in the velocity of early diastolic long-axis LV lengthening and the changes in the pattern of transmitral flow suggest impaired ventricular relaxation. These measures of cardiac function may be a useful index of normal cardiac ageing.

Keywords: ageing, ventricular function, left, systole, diastole, echocardiography, Doppler, elderly, longitudinal myocardial dysfunction, cardiac ageing

Introduction

Ageing affects all components of the heart (muscular, interstitial and vascular) [1]. Characteristic changes include left ventricular (LV) hypertrophy, myocardial fibrosis and alterations in coronary vasculature [2]. Previous in vivo human studies, mostly performed with the use of echocardiography, reported increased ventricular wall thickness, higher myocardial mass and little changes in LV size in older people with generally preserved global systolic function [3–5].
The normal myocardium is structurally and functionally heterogeneous. As a consequence of ventricular myocardium consisting of circular, oblique and longitudinal myocardial fibres [6], global LV function has several components—radial, circumferential and longitudinal. Recently, the use of Doppler tissue imaging (DTI), a relatively new echocardiographic technique that allows the reproducible measurement of the long-axis motion and deformation of the myocardium, has led to an increase in interest in the longitudinal component of myocardial function [7].

Impairment of long-axis myocardial function might precede development of global LV dysfunction in myocardial hypertrophy or ischaemia [8, 9]. Both these processes and other influences due to normal ageing might predispose the heart to the impairment of longitudinal myocardial function. This study was therefore designed to explore long-axis LV function as assessed with DTI in healthy older subjects.

Methods

Two hundred healthy individuals not taking any cardiovascular medication were identified from the lists of local general practitioners and asked to attend the cardiology department for review; 160 subjects (age 61±19 years, range 20–90 years) accepted. Subjects who had symptoms or a history suggestive of cardiovascular disease (including hypertension) or other chronic illnesses or took any regular medications (except painkillers) were subsequently excluded. All patients had a physical examination, electrocardiogram and echocardiogram and, again, patients with important abnormalities were excluded. The study was approved by the local research ethics committee and informed written consent was obtained from all the subjects.

Each subject underwent full echocardiographic examination including quantitative 2-dimensional colour-coded DTI using commercially available equipment (a GE Vingmed Vivid Five scanner equipped with 2.5 MHz phased array transducers). All Doppler echocardiographic recordings were obtained during normal expiration.

Left atrial diameter was measured at end-systole from B-mode guided M-mode echocardiographic images obtained in the parasternal long-axis view. Measurements of LV end-diastolic and end-systolic volumes were performed using the modified Simpson’s rule. LV ejection fraction was calculated with the standard formula.

Pulsed wave Doppler studies of transmitral flow were performed from an apical 4-chamber view with the sample volume positioned between the tips of mitral leaflets in diastole. Peak velocity of early filling (E) and peak velocity of atrial filling (A) were measured and the E/A ratio was calculated. To measure isovolumic relaxation time, the sample volume was placed between the anterior leaflet of the mitral valve and LV outflow tract and the deceleration time of early transmitral filling was calculated as the time between the peak of early filling and the upper deceleration slope extrapolated to the baseline.

Real-time 2-dimensional colour-coded tissue Doppler images were obtained in three apical views (four chamber, two chamber, and apical long-axis view) and stored digitally for subsequent offline analysis using Echopac 6.3 (GE Vingmed) software. Systolic (Sm), early diastolic (Em) and late diastolic (Am) velocities were measured at the lateral, septal, anterior, inferior, posterior and antero-septal sites of the mitral annulus and averaged, and Em/Am, E/Em and A/Am ratios were calculated. All measurements were done as the mean of two or three consecutive cardiac cycles.

Statistical analysis

Results are presented as mean±SD. An unpaired t test was used to compare the data between younger and older study groups. The data between older age subgroups were compared by analysis of variance followed by post-hoc analysis using the Newman–Keuls test. A P value less than 0.05 was considered to be significant. Univariate and multivariate regression analyses were used to assess the association between age and tissue Doppler-derived indices.

Results

Five subjects were excluded due to the unanticipated discovery of serious cardiac disease (two aortic stenosis, one mitral regurgitation, one aortic root dilatation and one left ventricular systolic dysfunction). Thirty-seven subjects with persistently elevated blood pressure were excluded.

Subjects were then split into two groups either below or on and above the median age (60 years). Fifty-eight individuals aged 40±13 years old formed the younger group and 60 individuals aged 73±8 years old composed the older group. Subject characteristics are presented in Table 1. Younger individuals had a higher body surface area (P=0.005) but there was no difference between groups in body mass index. Left atrial diameter was larger in older individuals (P<0.001), but we did not find any differences in LV volumes between the groups. LV ejection fraction was not different between the groups.

Analysis of the transmitral flow revealed significant differences in conventional Doppler indices used for the assessment of LV diastolic function. Isovolumic relaxation time was greater in older subjects (P=0.001). Peak E velocity of early transmirtal filling was lower (P<0.001) and peak A velocity of atrial filling was greater (P<0.001) in older subjects with a significant decrease in E/A velocity ratio (P<0.001).

Table 1 also shows mitral annular velocities measured with tissue Doppler imaging. We found lower systolic Sm (P<0.001) and early diastolic Em (P<0.001) velocities in the group of older subjects, while late diastolic Am velocity was greater (P=0.002). As a result, the Em/Am ratio was significantly lower in individuals of older age (P<0.001).

Appendices 1 and 2 (available as supplementary data on the journal website www.aging.oupjournals.org) illustrate typical profiles of Doppler-derived mitral annular velocities obtained in a younger and an older subject. There is a characteristic decline in Sm and Em velocities with an increase in Am velocity in the older subject.

Scatter plots showing the association between age and Sm (r=-0.44, P<0.001), Em (r=-0.80, P<0.001), Am (r=0.49, P<0.001) velocities and the Em/Am ratio (r=-0.78, P<0.001) are demonstrated in Figure 1. The relationship...
between age and the $E_m/A_m$ ratio was better described using a cubic curve regression model ($R^2=0.72$, $P<0.001$ for a cubic model versus $R^2=0.60$, $P<0.001$ for a linear model). The final independent tissue Doppler-derived indices that remained significantly related with age after multivariate regression analysis were $E_m$ and $A_m$ velocities ($R=0.83$, $R^2=0.691$).

The older subjects were further divided into three subgroups aged 60–69, 70–79 and ≥80 years old (Table 2). We found that there was a further increase in peak $A$ velocity of
transmitral filling in subjects 70–79 and ≥80 years old compared to the group of subjects aged 60–69 years with a corresponding decrease in the E/A velocity ratio. Deceleration time of early LV diastolic filling was prolonged in the oldest age subgroup.

There was also a trend to a further decrease in the velocity of longitudinal systolic shortening (Sm) and an increase in the velocity of late diastolic lengthening (Am) in individuals ≥80 years old. The velocity of early diastolic lengthening (Em) showed characteristic progressive deterioration with older age with a resulting decrease in Em/Am ratio.

**Discussion**

The ageing of the cardiovascular system is a complex process, which involves significant changes in the vascular bed as well as structural remodelling and functional adjustment of the heart [1]. It is also related to neurohormonal changes including activation of the renin–angiotensin system and elevated concentration of atrial natriuretic peptide [10].

At the subcellular level, ageing is associated with changes in excitation–contraction coupling mechanisms and diminished beta-adrenergic contractile response [11]. At the cellular level, cardiac ageing is characterised by a significant reduction of cardiomyocyte number with hypertrophy of remaining cells and an increase in interstitial tissue [2]. Accumulation of these adverse morphological changes could lead to deterioration of LV function at the organ level.

However, in this study we did not find any difference in echocardiographically measured LV ejection fraction between younger and older individuals. These data as well as data from other in vivo human studies [4, 12, 13] demonstrate that global LV systolic function does not deteriorate with normal ageing.

However, by measuring mitral annular velocities with DTI we have demonstrated a decline of longitudinal LV function with age. Both systolic and early diastolic velocities are reduced in older individuals. Systolic mitral annular Sm velocity is a simple and reliable measure of longitudinal LV systolic function [14, 15], and early diastolic Em mitral annular velocity is a preload-independent index of LV diastolic function [16, 17]. Late diastolic Am mitral annular velocity increases with age, reflecting age-related compensation of left atrial function to maintain LV filling.

Low systolic myocardial velocities have been reported in patients with ischaemic heart disease [18], hypertrophic cardiomyopathy and hypertension [19] with normal LV ejection fraction. Longitudinal LV function can be impaired in patients with heart failure (mostly older) and preserved global LV systolic function [20, 21]. The evidence that impaired longitudinal systolic function exists in normal ageing suggests that there might be common mechanisms involved in ageing and these cardiac diseases.

Systolic mitral annular velocity is not the only established index of longitudinal LV function. Echocardiographically measured mitral annular excursion has been a popular index in use since the late 1960s. Recent studies have shown a strong correlation between the two approaches for the assessment of long-axis LV function [22]. Both mitral annular velocities and mitral annular excursion also correlate well with LV ejection fraction [22, 23] and are representative of global LV systolic function. However, global LV function has three components (radial, circumferential and longitudinal) related to different layers of myocardial fibres (circular, oblique and longitudinal) [6], which may be non-uniformly affected by cardiac disease. Therefore, the relationship between measures of long-axis function and LV ejection fraction is non-linear and is affected by such additional factors as LV size, LV wall thickness and heart rhythm [23].

TDI can be also used for the assessment of other components of LV systolic function (e.g. radial contraction in parasternal views). However, such an approach has been marred by limited reproducibility of velocity measurements [24]. Currently, only the assessment of longitudinal velocities in apical views has been shown to be sufficiently reliable to be recommended for clinical use.

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**Table 2. Comparisons between older age subgroups**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>n</th>
<th>Body Surface Area (m²)</th>
<th>Body Mass Index (kg/m²)</th>
<th>Left Atrial Dimension (cm)</th>
<th>Left Ventricular End-Diastolic Volume (ml)</th>
<th>Left Ventricular End-Systolic Volume (ml)</th>
<th>Left Ventricular Ejection Fraction (%)</th>
<th>IV Ratio</th>
<th>Peak Early Diastolic Mitral Annular Velocity (cm/s)</th>
<th>Peak Late Diastolic Mitral Annular Velocity (cm/s)</th>
<th>Peak Systolic Mitral Annular Velocity (cm/s)</th>
<th>Peak Early Diastolic Mitral Annular Velocity/Am Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>60–69</td>
<td>22</td>
<td>1.79 ± 0.18</td>
<td>24.9 ± 2.3</td>
<td>4.0 ± 0.3</td>
<td>36 ± 10</td>
<td>67 ± 13</td>
<td>61 ± 7</td>
<td>91 ± 19</td>
<td>5.44 ± 1.06***</td>
<td>5.49 ± 1.60***</td>
<td>5.54 ± 1.06*</td>
<td>0.84 ± 0.26***</td>
</tr>
<tr>
<td>70–79</td>
<td>23</td>
<td>1.80 ± 0.17</td>
<td>26.1 ± 3.7</td>
<td>4.2 ± 0.4</td>
<td>39 ± 13</td>
<td>68 ± 19</td>
<td>59 ± 9</td>
<td>90 ± 27</td>
<td>5.28 ± 1.11***</td>
<td>4.45 ± 1.39***</td>
<td>5.28 ± 1.11***</td>
<td>0.80 ± 0.23</td>
</tr>
<tr>
<td>≥80</td>
<td>16</td>
<td>1.70 ± 0.19</td>
<td>25.6 ± 3.9</td>
<td>4.2 ± 0.5</td>
<td>43 ± 14</td>
<td>62 ± 15</td>
<td>58 ± 5</td>
<td>92 ± 22</td>
<td>4.15 ± 0.79</td>
<td>3.09 ± 1.1</td>
<td>4.15 ± 0.79</td>
<td>0.75 ± 0.20</td>
</tr>
</tbody>
</table>

*P < 0.05 between group 1 and group 2, **P < 0.05 between group 1 and group 3, ***P < 0.05 between group 2 and group 3.

BSA, body surface area; BMI, body-mass index; LAD, left atrial dimension; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; IVRT, isovolumic relaxation time; E, peak velocity of early transmitral filling; A, peak velocity of atrial transmitral filling; DT, deceleration time of early transmitral filling; Sm, peak systolic mitral annular velocity; Em, peak early diastolic mitral annular velocity; Am, peak late diastolic mitral annular velocity.
LV diastolic dysfunction commonly occurs in normal ageing. Both muscular and interstitial components are involved in the impairment of active and passive diastolic properties of the myocardium. Impaired calcium uptake by the sarcoplasmic reticulum of the cardiomyocytes is one of the mechanisms leading to slow and incomplete active ventricular relaxation in aged hearts [25], while the passive elastic properties of the myocardium are adversely affected by the expansion of the interstitium and alterations in collagen metabolism [26].

Characteristic changes in the pattern of LV diastolic filling with prolongation of isovolumic relaxation time and inversion of the ratio between peak velocities of early and atrial filling are traditionally associated with LV diastolic dysfunction [27]. In this study these findings were further confirmed by depressed early diastolic E pump mitral annular velocity in older subjects.

Early diastolic E pump mitral annular velocity is a relatively new index of LV diastolic function. It has some important advantages compared to conventional Doppler indices as it is less preload dependent and does not follow the U-pattern characteristic for load-dependent Doppler velocities of mitral and pulmonary venous flow [16]. Therefore, E pump velocity better reflects the genuine state of LV relaxation, even in patients with a compensatory increase in LV diastolic filling pressure.

Of many echocardiographic indices measured in this and other studies [28, 29], E pump velocity has the strongest negative linear correlation with age and might therefore be useful as a non-invasive echocardiographic marker of cardiac ageing. In one study [30], A pump velocity showed a marginally stronger correlation with age than E pump velocity. Combined tissue Doppler and conventional Doppler indices of LV diastolic filling also showed a progressing decrease (E pump/A pump ratio) or increase (E/E pump ratio) with age and can be used along with traditional indices to follow age-related changes in LV diastolic function.

In contrast to E pump velocity, late diastolic A pump mitral annular velocity increases with age. The main determinant of A pump velocity is left atrial function [30]. Age-related increase in A pump velocity as well as in transmitral peak A velocity indicate that augmentation of left atrial function with age is probably in response to deteriorating LV diastolic function. Morphologically this is accompanied by left atrial dilatation, suggesting activation of the Starling mechanism.

Selective impairment of longitudinal myocardial function with age might be due to predominantly subendocardial localisation of longitudinal myocardial fibres making them more susceptible to age-related haemodynamic overload as a result of increased stiffness of the vascular system, neurohormonal activation and impaired coronary circulation. They may also be affected earlier by interstitial and perivascular myocardial fibrosis.

Longitudinal myocardial function is related to the number of cardiomyocytes and the density of beta-adrenergic receptors [31]. Down-regulation of myocardial beta-adrenergic receptor density in failing human hearts is predominantly subendocardial [32]. A reduction in cardiac beta1- and beta2-adrenergic responses with decreases in both beta-adreno-ceptor subtype densities and a reduction in membrane adenylyl cyclase activity corresponding to the overall reduction in contractile response occur with ageing [33]. There is a negative relationship between interstitial fibrosis and S Sm and E Sm velocities [31]. Although there are no data in healthy older subjects directly correlating changes in the interstitial component of the myocardium with indices of long-axis ventricular function, previously well-documented age-related fibrosis [2, 26] could be responsible for a decrease in longitudinal myocardial function with age found in this study.

Although the results of the present study suggest that ageing is associated with impaired longitudinal LV systolic function, it is not translated into global LV systolic dysfunction. Therefore, there must be an augmentation in other components (radial or circumferential) of contractile ventricular performance to compensate for the deterioration in longitudinal LV systolic function. It is possible that such compensation becomes inadequate under stress and may therefore be a factor limiting cardiovascular reserve capacity in older people.

**Conclusions**

The present study demonstrates that normal cardiac ageing leads to low systolic mitral annular velocities, which suggests selective impairment of the longitudinal component of LV systolic function. Early diastolic mitral annular velocities also progressively decline with age in parallel with changes in the pattern of transmital flow indicative of impaired diastolic properties of the left ventricle. The observed characteristic changes in LV longitudinal function could serve as a surrogate measure of cardiac ageing.

**Key points**

- Global left ventricular systolic function is preserved with age.
- The velocity of long-axis systolic left ventricular shortening declines with age, indicating selective impairment of the longitudinal component of systolic contraction in older individuals.
- The velocity of early diastolic long-axis left ventricular lengthening decreases with age, which together with the transformation in the pattern of transmital flow are signs of age-related left ventricular diastolic dysfunction.
- Early diastolic mitral annular velocity shows the strongest correlation with age and may be a useful non-invasive echocardiographic marker of cardiac ageing.

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**Conflicts of interest**

None to declare.
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Secondary causes of restless legs syndrome in older people

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Abstract

Background: secondary causes of restless legs syndrome (RLS) have been reported to be more common in those with late-onset RLS. However, ‘late-onset’ in previous studies was defined as onset after 45 years.

Objective: to determine the prevalence of secondary causes of RLS and the relationship between aetiological factors and age of symptom onset in an older population.

Design: prospective study conducted over a 5-year period.

Participants: 80 consecutive non-related patients diagnosed with RLS.

Measurements: patients were assessed according to a standard protocol. Age at symptom onset, severity of symptoms, neurological findings and laboratory tests were examined.

Results: iron deficiency (serum ferritin <50 ng/ml) was present in 22% of patients with onset before 50 years, 39% of those with onset at 50 to 64 years and 58% in those with onset after 64 years (P=0.009). Clinical neuropathy was also more common in older-onset patients (P=0.08). Family history was positive in 39%, 23% and 8% of these groups, respectively (P=0.008).

Conclusion: secondary causes of RLS become more common and a positive family history less common with increased age of symptom onset.

Keywords: restless legs syndrome, elderly, iron, ferritin

Introduction

Restless legs syndrome (RLS) is a sleep disorder characterised by unpleasant leg sensations, which may be described as crawling, restless or fidgety in nature [1]. These sensations are felt deep within the limb and are usually bilateral; rarely, the arms may also be affected. Symptoms of RLS are invariably worse while resting and are particularly prominent at night. In more severe cases, symptoms may be present to some extent throughout the day. Moving the legs relieves discomfort, at least to some extent. The vast majority of patients with RLS also have repetitive jerking movements called ‘periodic movements of sleep’ (PMS) in the legs. PMS may repeatedly awaken the patient from sleep, although some are aware only that they sleep poorly at night or that their bed partner complains of being kicked. PMS are also common in older people without RLS or sleep disturbance [2].

RLS is a common and distressing condition that receives little attention in standard medical textbooks and is frequently misdiagnosed or unrecognised by physicians. Anxiety and depression are common consequences of RLS, and many patients report that their symptoms have been described as psychological in origin [3]. Accurate diagnosis of RLS is usually straightforward provided a good history is elicited from the patient. Even though muscle cramps and peripheral neuropathy often co-exist with RLS, patients...