Impaired subendocardial contractile myofiber function in asymptomatic aged humans, as detected using MRI

Joost Lumens,1,3 Tammo Delhaas,4 Theo Arts,3 Brett R. Cowan,2 and Alistair A. Young1

1Bioengineering Institute and 2Department of Medicine, University of Auckland, Auckland, New Zealand; and Departments of 3Biophysics and 4Physiology, Cardiovascular Research Institute Maastricht, Maastricht, The Netherlands

Submitted 18 January 2006; accepted in final form 18 April 2006

ADVANCING AGE is associated with several interrelated structural and functional changes in the myocardium, e.g., left ventricular (LV) concentric remodeling (14, 25), myocardial fibrosis (32), hypertension, and impairments in coronary hemodynamics (31). In humans, diastolic function is affected by aging, as evident in 1) a decrease of the E/A ratio, reflecting decrease of transmitial flow velocity in early diastole (E) relative to that during atrial contraction (A), and 2) a decrease of mitral annulus velocity during passive ventricular filling (13, 23). Although these changes with age also are expected to affect systolic mechanics of the LV wall, in many studies involving asymptomatic populations no impairment was found in global systolic function, as indicated by conservation of ejection fraction (EF), circumferential shortening, and longitudinal shortening (16, 19, 20, 22, 23, 34). The local character of some of the asymptomatic physiological changes may result in an increase of inhomogeneity in contractile myofiber function, causing loss of efficiency. In rats, focal areas of fibrosis were markedly more pronounced in aged hearts, particularly in the LV subendocardial region (2–4, 10). For example, subendocardial fibrosis and impairment of subendocardial perfusion due to hypertension may change the transmural distribution of contractile myofiber function.

The transmural difference in contractile myofiber function can be quantified with the ratio of LV torsion to endocardial circumferential shortening (torsion-to-shortening ratio; TSR) during the ejection phase (30). In model studies (6, 7), as well as in experimental studies on dogs (5) and healthy young adults (30), TSR was found to be a fixed number, with a small interindividual variance. Torsion is a result of equilibrium between torques caused by the oblique myofibers in the subepicardium and subendocardium (5, 6). In a midventricular LV wall segment (Fig. 1), the myofibers at midwall are circumferentially oriented, whereas in the subepicardial and subendocardial layers, the myofibers follow left-handed and right-handed helical pathways, respectively (15, 27). During contraction, the subepicardial myofibers are dominant over the subendocardial myofibers, because they act over a larger radius. Thus the subendocardium partly counteracts torsional motion as induced by the subepicardium. Transmural differences in myofiber shortening as a result of ejection are compensated for by the net amount of torsion, which reduces subendocardial myofiber shortening and amplifies subepicardial myofiber shortening. In normal subjects, a fixed amount of torsion per amount of ejection results in homogeneity of myofiber shortening (1, 5, 6, 12, 30).

With impairment of subendocardial contractile function, counteraction of torsion by contraction of the subendocardial myofibers is less effective, causing net torsion to increase. Thus TSR increases with impairment of contractile function in the subendocardial layers relative to that in the subepicardial layers (12, 30).

In the present study, we investigated whether aging may be associated with changes in the transmural distribution of contractile function. If so, TSR is expected to change, whereas other parameters of systolic cardiac function may remain unaffected. Thus, in a group of asymptomatic aged volunteers not showing clinical signs of cardiac pathology, TSR was determined noninvasively with the use of MRI. Tagged mag-
AJP-Heart Circ Physiol • VOL 291 • OCTOBER 2006 • www.ajpheart.org

Fig. 1. Schematic representation of a midventricular left ventricular (LV) wall segment, visualizing the deformation of the LV wall during ejection. Contraction is considered to be composed of 2 modes of motion, i.e., ejection and torsion. With ejection in the absence of torsion (bottom left), myofibers would shorten more in the subendocardium (endo) than in the subepicardium (epi) because of incompressibility of the wall. In the hypothetical case of torsional deformation in the physiological direction, in the absence of ejection (top right), myofibers would shorten in the subepicardium at the cost of lengthening of the subendocardial myofibers, because of their specific helical orientations in the LV wall. Normally, a tuned amount of torsion per amount of ejection results in transmural homogeneity of myofiber shortening (bottom right).

MATERIALS AND METHODS

Approval for the study was obtained from the Auckland Human Subject Ethics Committee, and written informed consent was obtained from all participants. The investigation conforms to the principles outlined in the Declaration of Helsinki.

Subjects. Subjects were respondents to advertisements within the University of Auckland. Examinations were performed as part of a larger study on the effect of aging on ventricular mechanics (13, 23). Subjects were included only if no evidence of preexisting cardiac disease or other significant coexisting illness was found in a clinical examination. Exclusion criteria included a history of hypertension, diabetes, ischemic or valvular heart disease, regular use of medication for cardiovascular illness, or a resting blood pressure >160/90 mmHg. On the 12-lead ECG, atrial fibrillation, bundle branch block, pathological Q waves, left ventricular hypertrophy (LVH), or changes consistent with myocardial ischemia resulted in exclusion, as did any significant valvular abnormality, impaired systolic LV function, or LVH on the transthoracic echocardiogram. In a total of 31 subjects, an aged group [n = 16, ages 60–74 yr, mean 68.8 (SD 4.4) yr] and a young control group [n = 15, ages 19–26 yr, mean 23.2 (SD 2.6) yr] were distinguished. In both groups, ~75% of the subjects were male.

MRI protocol. Subjects were scanned in the supine position with a Siemens 1.5 Tesla Vision MRI scanner and a phased array surface coil. Three scout scans were performed to determine long and short axes of the left ventricle. Six short-axis slices were acquired, equally spaced between the apex and the basal plane. The extreme apical and basal image planes were positioned at the apical endocardium and at the mitral valve plane, respectively. For contouring purposes, standard turboFLASH cine MRI images were obtained (scan parameters: slice thickness, 8 mm; in-plane resolution, 1 mm/pixel; temporal resolution, 40 or 50 ms, depending on subject’s heart rate; TE/TR = 4.0/8.9; 128 × 256 image matrix). For motion analysis, tagged images were acquired at the same sections and using the same parameters, except for an increased temporal resolution of 35 or 45 ms (depending on heart rate). A segmented k-space version of the spatial modulation of magnetization (SPAMM) tagging sequence was used to create a tag grid with a spacing of 8 mm (8, 35). View sharing was used to reconstruct 15–27 time frames per cardiac cycle. Breath holds of ~15 s were applied to eliminate respiratory motion artifacts. The images covered ~85–90% of the cardiac cycle after ECG trigger.

Image analysis. The MR tagged images were analyzed off-line for each time frame. Custom software using Matlab 7.0 (MathWorks, Natick, MA) was used to quantify LV displacement, torsion, and endocardial circumferential shortening from the acquired images. In all slices, the LV wall was manually outlined in a single midsystolic reference frame of the nontagged cine images (Fig. 2, step 1). The papillary muscles were excluded from the analysis. Subsequently, the contours were projected on the corresponding tagged MR image (Fig. 2, step 2). Changes in two motion modes, i.e., cavity cross-sectional area and angular rotation of the LV wall, were determined using a least-squares fit on the displacement data in the outlined region of the LV wall during the imaged part of the cardiac cycle (Fig. 2, step 3). Displacement maps were derived from the tagged images by using the correlation interpolation technique previously described for pulsed ultrasonic echo signals (11). With this technique, displacement components were obtained for the two perpendicular line grids, resulting in two-dimensional (2-D) displacement maps of the cardiac cross section as a function of time, in the same way as previously done by Van der Toorn et al. (30) and Delhaas et al. (12).

Motion analysis. Using the obtained 2-D displacement information, we calculated rotation α of the LV wall as the average rotation about the centroid of the wall cross section. The change of cavity area was calculated as the radial material flux, being radial displacement of the midwall contour, multiplied by the length of this contour. Cavity area A_cav was estimated as the sum of manually outlined cavity area in the midsystolic frame and the change of this area relative to the midsystolic reference frame in every other frame. For the midsystolic reference frame, wall area A_wall was determined as the area between the epicardial and endocardial contours in the corresponding cine MR images (Fig. 2, step 1).

Torsion T, defined as the shear angle on the epicardial surface (5), was calculated for each slice pair as the longitudinal gradient in rotation angle α, multiplied by the epicardial radius R_epi (Fig. 2, step 4), using the following approximation:

\[ T = \frac{(\alpha^2 - \alpha'^2)}{d} \cdot \frac{(R_{epi}^2 + R_{epi}^2)}{2} \]  \hspace{1cm} (1)

where a and b refer to the lower and upper slice, respectively, and d represents interslice distance. R_epi was approximated as follows:

\[ R_{epi} = \sqrt{\frac{A_{wall} + A_{cav}}{\pi}} \]  \hspace{1cm} (2)

Following the method of Van Der Toorn et al. (30), endocardial natural circumferential strain ε_{inser} was quantified as one-half the
The most apical and basal slices were excluded because of artifacts related to commonly occurring out-of-plane motion of those parts of the left ventricle during part of the cardiac cycle. TSR was calculated as the median value of the change in torsion during all time intervals over all sections, divided by the corresponding interval of $\varepsilon_{\text{inner}}$.

**LV mass, pressure, and volume.** For all subjects, LV mass, body surface area (BSA), systolic blood pressure (SBP), diastolic blood pressure (DBP), end-diastolic LV volume (EDV), and end-systolic LV volume (ESV) were reported previously by Oxenham et al. (23). Mean end-diastolic LV wall thickness (LVWED) and end-diastolic LV inner diameter (LVEDd) were measured in the midventricular cine MR slice. LVWED was defined as the difference between the mean endocardial and epicardial radii.

**Statistical analysis.** Differences in TSR, peak LV torsion, and endocardial circumferential ejection strain between both groups were analyzed for significance with the use of a two-tailed $t$-test, with unequal variances and a significance level of 5%. Values are presented as means (SD). An $F$-test was used to test for equality of standard deviation of TSR between both groups. An analysis of covariance was performed to determine the influence of the LV mass-to-EDV ratio, LVWED, LVEDd, SBP, and DBP on TSR in the aged compared with the young group.

**RESULTS**

As reported previously (23), no significant differences in LV mass, LVEDd, EF, and ESV were found between the two age groups (Table 1). In the aged group, we found mild though significant changes in EDV ($-16\%$, $P = 0.031$), LVWED (15\%, $P = 0.009$), and LV mass-to-EDV ratio (23\%, $P = 0.006$), indicating mild concentric hypertrophy. Both SBP and DBP were significantly elevated in the aged group.

In Fig. 3, typical time courses of rotation angle are shown for the four short-axis slices used for TSR calculation (Fig. 3, slices 1–4). In early systole, the rotation angle of all slices increased in all subjects, indicating a counterclockwise rotation of the whole heart, when viewed from the apex. During ejection, rotation angles dispersed, resulting in a gradual transition of counterclockwise rotation of the apex to clockwise rotation of the base. After isovolumic relaxation, rotation angles generally fused to the common diastolic level. During the ejection phase, the time courses of torsion as well as the time courses of endocardial circumferential strain were quite

### Table 1. LV mass, volume, and pressure measurements

<table>
<thead>
<tr>
<th></th>
<th>Young</th>
<th>Aged</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>15</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>LV mass, g</td>
<td>142 (34)</td>
<td>145 (38)</td>
<td>0.82</td>
</tr>
<tr>
<td>LV mass-to-BSA ratio, g/m²</td>
<td>77 (11)</td>
<td>81 (29)</td>
<td>0.60</td>
</tr>
<tr>
<td>LVWED, mm</td>
<td>10.0 (1.1)</td>
<td>11.5 (1.7)</td>
<td>0.009*</td>
</tr>
<tr>
<td>LVEDd, mm</td>
<td>46.5 (3.1)</td>
<td>44.1 (5.0)</td>
<td>0.12</td>
</tr>
<tr>
<td>EF, %</td>
<td>70.7 (3.0)</td>
<td>69.3 (6.6)</td>
<td>0.45</td>
</tr>
<tr>
<td>EDV, ml</td>
<td>138 (27)</td>
<td>116 (27)</td>
<td>0.031*</td>
</tr>
<tr>
<td>ESV, ml</td>
<td>40 (9)</td>
<td>36 (13)</td>
<td>0.25</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>116 (15)</td>
<td>145 (16)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>62 (6)</td>
<td>84 (10)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>LV mass-to-EDV ratio</td>
<td>1.03 (0.10)</td>
<td>1.27 (0.30)</td>
<td>0.006*</td>
</tr>
</tbody>
</table>

Values are presented as means (SD); $n$ = no. of subjects. For $P$ values, differences were analyzed for significance with a two-tailed $t$-test, supposing unequal variances. LV, left ventricular; BSA, body surface area; DBP, diastolic blood pressure; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LVEDd, left ventricular end-diastolic diameter; LVWED, left ventricular end-diastolic wall thickness; SBP, systolic blood pressure. *$P < 0.05$, mean value aged vs. young.
similar for all sections (sections A–C in Figs. 4 and 5, respectively). When torsion was plotted as a function of endocardial circumferential strain, the relation was practically linear with a similar slope for all sections (Fig. 6) during the ejection phase. Peak LV torsion was significantly larger \( (P < 0.0001) \) in the aged group \( 0.158 \) (SD 0.030) than in the young group \( 0.119 \) (SD 0.026). Ejection strain in the circumferential direction was not significantly different \( (P = 0.13) \) between the young \( 0.400 \) (SD 0.055) and aged groups \( 0.366 \) (SD 0.064). Figure 7 shows that both the mean value \( (P = 0.0004) \) and the standard deviation \( (P = 0.006) \) of TSR were significantly higher in the aged group \( 0.47 \) (SD 0.12) than in the young group \( 0.34 \) (SD 0.05). Within the groups, no significant correlation was found between TSR and the LV mass-to-EDV ratio or LVWED (Fig. 8), used as measures of LVH. In addition, no significant correlation was found between TSR and SBP or DBP.

**DISCUSSION**

In a young and an aged group of asymptomatic volunteers, the TSR during the ejection phase was determined noninvasively using MR tagging. In the aged group, both the mean value and standard deviation of TSR were significantly higher than in the young group. A supranormal value of TSR indicates contractile function to be less in the subendocardium than in the subepicardium. Other indexes of systolic LV function, such as ESV and EF, were not significantly different. The findings in the present study suggest that aging is associated with a decrease of contractile function in the subendocardium relative to that in the subepicardium, without obvious loss of global LV pump function.
The current study shows a significantly ($P = 0.0004$) elevated mean value of TSR in the aged group, which may be explained as follows. In previous studies on normal young subjects, i.e., humans (1, 30) as well as animals (5), the consistent value of TSR indicated that the transmural distribution of myofiber strain is uniform. Because TSR also depends on the transmural distribution of myofiber angulation, the latter finding also suggests that myocardial fiber structure is quite universal for different species, humans inclusive. Elevation of mean TSR among aged asymptomatic adults suggests that aging is associated with a change in the transmural distribution of contractile myofiber function (30). The higher value of TSR in the aged group may be a result of subclinical impairment of subendocardial contractile function, due to interrelated changes in the cardiac tissue such as subendocardial fibrosis (2, 10, 24), asymptomatic subendocardial infarction (29), or impairment of subendocardial perfusion (12, 29, 30). All these circumstances may result in loss of subendocardial contractile function, which is consistent with the hypothesis that homogeneity of myofiber work in the LV wall decreases with age, as indicated by an increase of TSR.

Besides the mean value of TSR, its standard deviation also was significantly ($P = 0.006$) increased in the aged group. The young group may be considered as a control group, having a homogeneously healthy, pristine myocardial tissue, as indicated by the small standard deviation of TSR relative to its mean value (SD/mean = 0.15). In the aged group, contractile function of the myocardium appears less homogeneously distributed while also showing more interindividual variations. Seemingly, with age, subclinical pathological incidents causing local loss of contractile function occur on a regular basis. Because of enhanced vulnerability of the subendocardium for such incidents (9, 18, 21), it is on the average more affected than the subepicardium, explaining the increase of average TSR. Because frequency and severity of incidents vary interindividually, the increase of TSR varies largely, as indicated by the significant increase of the standard deviation of TSR in the elderly.

The characteristics of TSR in elderly appear similar to those in patients having aortic stenosis (12, 30), albeit to a lesser degree. In these patients, both TSR and its relative standard deviation were increased significantly [0.85 (SD 0.26), $P < 0.001$]. Just as in the aged subjects of the present study, the increase of TSR in patients with aortic stenosis was attributed to enhanced vulnerability of the subendocardium (30). The increase of the standard deviation of TSR was attributed to variation in severity of pathology. After repair of the aortic valve, TSR decreased to nearly normal values, indicating that subendocardial function was mostly recovered. The recovery of TSR can be explained by improved supply-demand ratio of subendocardial coronary perfusion after valve repair. Strikingly, in all TSR measurements known so far, TSR has never been found to decrease below normal, indicating that subepicardial contractile function never decreases below subendocardial function. This finding is in agreement with known physiology of coronary perfusion, in that no pathological situations are known in which subepicardial function would be affected more than subendocardial function.

The increase of the LV mass-to-EDV ratio suggests mild concentric hypertrophy, together with mild hypertension (Table 1). One may wonder whether this hypertrophy and hypertension may explain the increase of TSR while leaving the transmural distribution of contractile function unaffected. Within the young group, as well as within the aged group, no significant relation was found between TSR and LV mass-to-EDV ratio or LVEDd, indicating that concentric hypertrophy alone was not affecting TSR significantly.

Patients with concentric hypertrophy are reported to have elevated torsion (28), whereas EF is normal or slightly diminished (25), thus indicating an increase of TSR. This finding is not surprising, because both hypertension and concentric hypertrophy are risk factors for coronary artery diseases, likely resulting in subendocardial damage (17, 18, 25) and, hence, an increase in TSR. Furthermore, eccentric hypertrophy does not significantly affect torsion and ejection fraction (28).

![Fig. 7](http://example.com/fig7.png)  
**Fig. 7.** TSR values (●) in the young and aged groups of asymptomatic volunteers. For both groups, mean TSR (□) is indicated with standard deviation (error bars). Note the relatively narrow range of TSR in the young control group. *$P < 0.05$, mean TSR in aged vs. young group. #$P < 0.05$, standard deviation TSR in aged vs. young group.

![Fig. 8](http://example.com/fig8.png)  
**Fig. 8.** Scatter plots of TSR as a function of the ratio of LV wall mass to end-diastolic volume (LV mass-to-EDV ratio; A) and as a function of end-diastolic LV wall thickness (LVWED; B). Note that no significant relation was found between TSR and the LV mass-to-EDV ratio or between TSR and LVWED in either separate age group.
In a theoretical study of torsion, with the use of a model of fiber mechanics in the cardiac wall (5), a 40% increase of wall thickness resulted in an increase of TSR by ~10%. Comparing the young group with the aged group in our study, wall thickness was increased by ~15% (Table 1), thus explaining an increase of TSR by ~6%. The measured increase of TSR in the aged group was much larger (38%).

Summarizing, we have no indications for a direct relationship between hypertrophy alone and TSR. An increase of TSR is considered indicative for a decrease of function in the subendocardium compared with that in the subepicardium.

In the current study, TSR in the young group was found to be somewhat lower [0.34 (SD 0.05)] than previously reported values. The normal value for TSR has been found to be invariant to loading and universal to all normal left ventricles, although slight differences in the mean value have been reported. In a mathematical model study (5), assuming a cylindrical geometry, the optimum value of TSR, achieving a uniform transmural distribution of contractile work, was 0.42. In an echocardiography study on normal dogs (5), TSR was found to be 0.43 (SD 0.04). In an MRI study on nine healthy young humans, Aalen et al. (1) reported a value of 0.38 (SD 0.05). Similarly, in a human study, Van Der Toorn et al. (30) reported a value of 0.44 (SD 0.07). The differences are likely due to differences in methodology and interobserver variability in the placement of epicardial and endocardial contours. These systematic differences are unlikely to affect the significance of the differences in TSR as found between the young and aged asymptomatic adults, because the same analysis has been applied to both the young and the aged.

To estimate the accuracy of the part of the image analysis method used to derive displacement maps from the tagged MR images, we tested the current analysis method in a simulation representing the left ventricle of a healthy young adult with known physiological values of LV rotation, torsion, and contraction (see APPENDIX for details). In summary, this test showed that our method of analysis overestimated TSR by 2.8%. This overestimation is much smaller than the standard deviation, as measured in the group of young controls. Thus the TSR calculation is not significantly affected by inaccuracies in the method of displacement calculation.

**Study limitations.** Although the studied population showed no evidence of ischemic heart disease (IHD) on MRI and echocardiography tests, there was no conclusive evidence obtained for the absence of asymptomatic IHD. Thus subclinical IHD may have partly accounted for the differences seen between the groups. Previous studies have shown that our asymptomatic aged subjects may fall into an increased risk category for IHD (26, 33). A larger cohort with clinical data such as smoking, cholesterol, and stress test results should therefore be studied to evaluate the effect of asymptomatic ischemic heart disease on the transmural distribution of contractile myofiber function.

In conclusion, in the present study, MR tissue tagging data were analyzed to quantify 2-D motion in parallel LV short-axis cross sections during the cardiac cycle. From the 2-D displacement data, LV torsion and endocardial circumferential strain were determined, resulting in an estimate of the transmural difference in myofiber shortening. Differences in the transmural distribution of myofiber shortening were assessed noninvasively in a group of asymptomatic aged volunteers and compared with those assessed in a control group of asymptomatic young volunteers. Systolic TSR was significantly increased in the aged subjects, with subclinical degrees of LV hypertrophy and hypertension that could not be correlated to the increase in TSR. There were no significant differences in other indexes of systolic LV function such as ESV and EF. Apparently, in the asymptomatic aged group, contractile function in the subendocardium is deteriorated relative to that in the subepicardium in the absence of obvious signs of cardiac pathology. This loss of function may be attributed to one or several subclinical incidents, possibly related to deteriorated subendocardial coronary perfusion or subendocardial fibrosis.

**APPENDIX: ERROR ANALYSIS**

We applied the 2-D deformation analysis procedure to a simulated test case with known rotation, torsion, contraction, and TSR. Four short-axis slices of a thick-walled incompressible cylinder represented the human left ventricle in a model. For each slice, a grid-tagged reference image of each slice was generated with a tagline spacing of 8 mm. Subsequently, a time sequence of deformed images was generated by deforming the reference image with mathematically generated displacement fields, simulating normal contraction and torsion, as measured earlier in adult healthy humans by Van Der Toorn et al. (30). Gaussian noise (signal-to-noise ratio of 18 dB), representative of the noise in the MR tagging data used in this study, was added. After the method of analysis was applied to obtain displacement maps from the mathematically generated tagged images, the error was estimated by comparison of the calculated TSR with the simulated TSR value.

In Table 2, the results of the error analysis are presented. Torsion as well as ejection strain ($\Delta$E$_{eject}$) appeared to be slightly underestimated, whereas TSR was slightly overestimated by the current method of analysis.

**GRANTS**

We gratefully acknowledge the support of the Health Research Council of New Zealand and Netherlands Heart Foundation Grant 2000T036.

**REFERENCES**
