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# Aging alters patterns of regional nonuniformity in LV strain relaxation: a 3-D MR tissue tagging study

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**Fonseca, Carissa G., Helen C. Oxenham, Brett R. Cowan, Christopher J. Occleshaw, and Alistair A. Young.** Aging alters patterns of regional nonuniformity in LV strain relaxation: a 3-D MR tissue tagging study. *Am J Physiol Heart Circ Physiol* 285: H621–H630, 2003. First published April 10, 2003; 10.1152/ajpheart.01063.2002.—Although age-related impairment of diastolic function is well documented, patterns of regional tissue relaxation impairment with age have not been characterized. MRI tissue tagging with a regional three-dimensional (3-D) analysis was performed in 15 younger (age 19–26 yr) and 16 older (age 60–74 yr) normal, healthy volunteers. The peak rate of relaxation of circumferential strain ($R_C$) was decreased in the older group (on average, 105 ± 28 vs. 163 ± 18 %/s for older vs. younger, mean ± SD, $P < 0.001$) to a greater extent in the lateral wall than in the septum ($P = 0.016$) and to a greater extent in the apex than in the base ($P < 0.001$). Peak rate of relaxation of longitudinal strain ($R_L$) was also reduced with age (94 ± 27 vs. 155 ± 18 %/s, $P < 0.001$) to a greater extent in the apex than in the base ($P < 0.001$). Both $R_C$ and $R_L$ were greater in the apex than in the base only in the younger subjects ($P < 0.001$ for each). Peak rate of torsion reversal ($R_T$) was reduced with age (74 ± 16 vs. 91 ± 15 degrees/s, $P = 0.006$) to a greater extent in the base than in the apex ($P = 0.035$). An increase in regional asynchrony in time to $R_C$ and time to $R_L$ ($P < 0.001$ for each), but not time to $R_T$, occurred with age. Thus patterns of regional nonuniformity of myocardial relaxation are altered in a consistent fashion with aging.

myocardium; magnetic resonance imaging; diastole; elderly; left ventricular

MARKED CHANGES IN DIASTOLIC FUNCTION are known to occur in normal healthy older people, whereas indexes of systolic function are generally well preserved (12, 24, 33). Changes in myocardial relaxation associated with age include a reduced early peak filling rate relative to the atrial component of filling (reduced E/A ratio) (8, 23, 32, 44), a prolongation of isovolumic relaxation time (47), and an increased time to peak filling rate (6, 14).

The processes contributing to these changes have yet to be fully elucidated but may be related to regional heterogeneity in the timing and magnitude of left ventricular (LV) diastolic filling. Whereas global LV function has been extensively studied, there have been relatively few reports on regional myocardial function during diastole. It is evident, however, that both normal (5, 7) and dysfunctional (15, 25) LVs are regionally heterogeneous with respect to structure and function (18). Detailed regional information is required to determine how structural and mechanical changes that occur in localized portions of the myocardium contribute to the changes observed in global function. Furthermore, changes due to normal aging must be characterized before pathological changes in regional function can be identified.

Studies that have employed techniques such as radionuclide angiography (6, 14) and echocardiography (49), in normal healthy human subjects, suggest that age-related changes in diastolic function occur in a regionally heterogeneous way. The increase in regional diastolic filling asynchrony and nonuniformity with age that these studies have demonstrated is thought to contribute to the age-related alterations observed in global LV diastolic function (44, 47). However, radionuclide angiography requires the injection of radioactive isotopes, and measurements of LV chamber dynamics do not directly quantify myocardial relaxation. Strain rate imaging, a technique derived from echocardiographic tissue Doppler imaging, can provide direct, noninvasive measures of myocardial strain relaxation on a regional basis (9, 11, 21, 49). However, the components of strain relaxation that can be quantified are limited to those in the direction of the ultrasound beam, and not all regions of the ventricle can typically be examined. Furthermore, the effect of through-plane motion on these measurements remains unknown.

Regional myocardial strain can be directly quantified noninvasively by using magnetic resonance (MR) tissue tagging (4, 56). This method creates tags by presaturating planes of tissue, perpendicular to the subsequent imaging planes, with a short burst of radiofrequency pulses. The "tag planes" appear on the image as a dark grid pattern that moves and deforms along with

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the myocardium. Analysis of this deformation then allows direct, noninvasive measurement of regional myocardial motion with high accuracy (54). Unique information is thereby obtained regarding rotational, circumferential, and longitudinal shortening and lengthening through most of the cardiac cycle (51).

MR tissue tagging studies have characterized the regional nonuniformity of systolic function in the normal LV (5, 53). Diastolic relaxation parameters have also been investigated (38). One such parameter, the rate of relaxation of LV torsion, has been shown to be relatively independent of preload and afterload (10) and to be reduced in disease (45). During contraction, the LV myocardium twists in the anticlockwise direction at the apex and in the clockwise direction at the base (as viewed from the apex), thereby literally wringing out the blood. Diastolic untwisting, or recoil of this "torsion," is thought to be related to the decay of LV pressure, thus creating suction and rapid early filling (10, 31).

Recently, Kuijer et al. (27) quantified regional three-dimensional (3-D) diastolic strain evolution in 10 normal volunteers, demonstrating the feasibility of MR tissue tagging to measure regional strain relaxation parameters. Global tissue relaxation measurements, made using this technique, have shown a significant delay and a reduction in the rate and extent of myocardial relaxation in older people (37). However, changes in regional myocardial relaxation due to aging have not been assessed using this technique.

We used tagged MRI to quantify regional 3-D diastolic strain and strain relaxation rates in old and young people. We hypothesized that regional nonuniformities in myocardial strain relaxation are altered in a consistent pattern with normal aging. The aims of this study were therefore to *1*) quantify the differences in myocardial relaxation in the different regions of the LV and *2*) determine the effect of aging on these regional nonuniformities.

## METHODS

### *Subjects*

Subjects were recruited into the study after responding to advertisements within the University of Auckland. Approval for the study was obtained from Auckland Human Subject Ethics Committee, and written informed consent was obtained from all participants. Subjects were included only if a clinical examination, transthoracic echocardiogram, and 12-lead ECG showed no evidence of preexisting cardiac disease or other significant coexisting illness. 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 above 160/90 mmHg. On the 12-lead ECG, atrial fibrillation, bundle branch block, pathological Q waves, LV hypertrophy, or changes consistent with myocardial ischemia resulted in exclusion, as did any significant valvular abnormality, impaired systolic LV function, or LV hypertrophy on the transthoracic echocardiogram. Transmitral Doppler echocardiography was performed successfully in all subjects except for two in the younger group.

A total of 31 subjects were scanned: 15 were classified as "younger" (age 19–26 yr, mean 22.3 yr), and the remaining 16 subjects were classified as "older" (age 60–74 yr, mean 68.8 yr). Approximately 75% of each group was male.

### *MRI Protocol*

All of the MR tagging studies were performed with subjects in the supine position with the use of a Siemens 1.5 Tesla Vision MRI scanner and a phased array surface coil. A segmented k-space version of the spatial modulation of magnetization (SPAMM) tagging sequence was used to create a tag grid in the images with a spacing of 8 mm and a width of ~1 mm. Tagged images were acquired in eight or nine short-axis slices, equally spaced from apex to base, and six long-axis slices at equal angular intervals around the central axis of the LV. View sharing was used to reconstruct 15–27 time frames per cardiac cycle with a breath-hold duration of 15–19 beats (scan parameters: slice thickness, 8 mm; in-plane resolution, 1 mm/pixel; temporal resolution, 35 or 45 ms, depending on subject's heart rate; TE/TR = 4.0/8.9; 128 × 256 image matrix). All images were prospectively gated, and therefore images could not be acquired during the last 10–15% of the cycle, to allow for detection of the R wave trigger. Tagged MR images from a typical subject in the older age-group are shown in Fig. 1. Tags could be visualized and tracked throughout the imaged portion of the cardiac cycle.

### *Image Analysis*

The images were stored digitally and analyzed off-line with a custom computer software package that incorporates a finite element model (54) to represent the geometry of the LV.

*Guide point modeling.* The geometry of the LV was defined using guide point modeling (52). In this technique, 3-D models are fitted interactively to guide points placed on the boundaries by the user, enabling fast reconstruction of LV geometry in all frames.

*Tag tracking.* Tag stripes were located and tracked using a semiautomated tracking procedure based on an active contour model (54). The tag stripes were tracked through the 15–19 images in each slice to determine the exact position of several hundred points in the myocardium through most of the cardiac cycle.

*Reconstruction of 3-D motion.* Finite element models were fitted to the tracked tag stripes using previously described methods (54). The model, which deforms to fit the displacement of the MR tags, consists of 16 elements, each with cubic interpolation in the circumferential and longitudinal directions. Through-plane motion and out-of-plane shears were accounted for by fitting the model to long- and short-axis data simultaneously. Previous validation experiments using a silicone gel model have shown that the tag analysis method described above produces accurate, unbiased estimates of displacement and shortening (54). The model was interrogated to provide regional circumferential and longitudinal shortening strains and torsional shear strain at each frame using standard continuum mechanics methods (13).

### *Myocardial Strains*

In each of the 16 standardized LV myocardial regions (42), we determined peak values for circumferential and longitudinal strains and torsion as well as the time (in ms) from end diastole (ED) to peak value. By convention, ED is 0 ms, and each frame is taken at 35- or 45-ms intervals after ED, depending on temporal resolution.

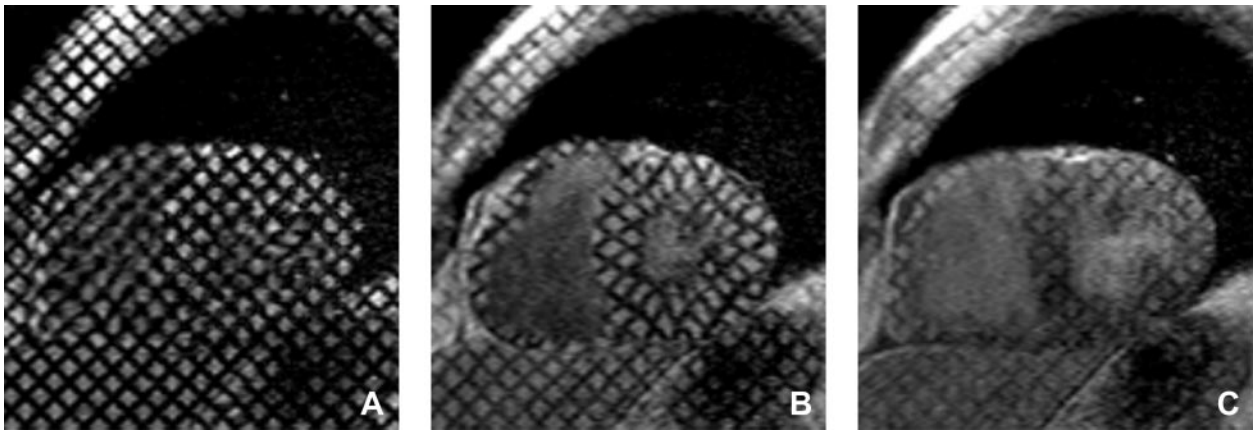


Fig. 1. Short-axis tagged magnetic resonance (MR) images at the midventricular (mid) level for a typical subject in the older group showing good tag persistence throughout the cardiac cycle. *A*: end diastolic, 45 ms; *B*: end systolic, 315 ms; *C*: late diastolic, 675 ms.

Circumferential ($\%s_C$) and longitudinal strains ($\%s_L$) were calculated as the percent change in length of small line segments, initially (i.e., at ED) oriented in the circumferential and longitudinal directions, respectively, and were calculated from the Lagrangian strain tensor $\boldsymbol{E}$ as follows (13)

$$\%s_C = [\sqrt{(1 + 2E_{CC})} - 1] \times 100\% \text{ and}$$

$$\%s_L = [\sqrt{(1 + 2E_{LL})} - 1] \times 100\%$$

Torsional shear strain (see Fig. 2) was calculated as the change in angle between small line segments orientated longitudinally and circumferentially at ED (13, 51). This torsion angle ($\alpha_{CL}$) was calculated from the strain tensor $E$ as follows (13)

$$\sin\alpha_{CL} = \frac{2E_{CL}}{(\sqrt{1 + 2E_{CC}})(\sqrt{1 + 2E_{LL}})}$$

$E_{CC}$, $E_{LL}$, and $E_{CL}$ represent the circumferential, longitudinal, and circumferential-longitudinal shear components, respectively, of the Lagrangian strain tensor.

The peak systolic strain rate and the peak rate of diastolic relaxation of strain were calculated by using a central difference formula. The maximum systolic strain rate is given by the peak rate of change of strain measured during systole, and the maximum diastolic strain relaxation rate is given by the peak rate of change of strain measured after peak strain. The time from ED to peak relaxation rate was also calculated.

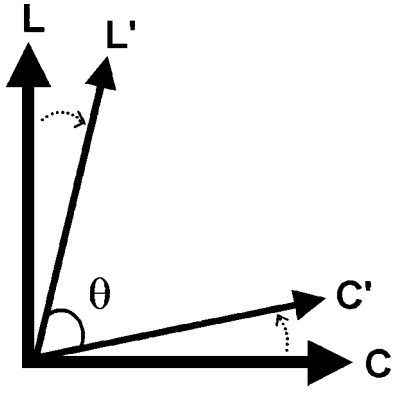


Fig. 2. Torsion is defined as the change in angle ($\alpha_{CL}$) between small line segments oriented in the circumferential (C) and longitudinal (L) directions at end diastole (initially 90 degrees) to the angle ($\theta$) between the same line segments (C′ and L′) at a later time $t$. Thus $\alpha_{CL} = 90 - \theta$ degrees.

Indexes of regional asynchrony, with respect to time to peak strain and torsion and time to peak rate of relaxation, can be obtained by calculating the absolute value of the difference between the global average and the value for each of the 16 regions and then by calculating the average of these 16 differences (6, 14, 50). An increase in the index of regional asynchrony would indicate increased regional heterogeneity with respect to time to peak strain and time to peak relaxation.

*Statistical Analysis.* Data were analyzed using the SYSTAT software package (version 10; SPSS). All data are presented as means ± SD. A two-factor multifactorial analysis of variance (MANOVA) was performed to examine the interaction between age and region. A significant interaction effect implies a significant difference in the pattern of regional heterogeneity due to age.

Strains at all tracked tag points were averaged into 16 standard LV myocardial regions (42). To test for regional differences longitudinally from the apex to base, we averaged the 16 regions into three longitudinal levels (apex, midventricle, and base, each averaged over all circumferential regions). Similarly, to test for circumferential differences, we averaged the 16 regions into four circumferential regions (septal, posterior, lateral, and anterior, each averaged over all longitudinal regions). Thus, for each strain parameter, two MANOVAs were performed, one testing the longitudinal variation and the other testing the circumferential variation.

Where a significant interaction existed between age and region, the following pairwise comparisons were performed. Between groups, each region in the older group was compared with the corresponding region in the younger group. Thus, for the three longitudinal levels or the four circumferential regions, the $P$ values have been corrected in Bonferroni fashion for three or four tests, respectively. Within each age group, comparisons between the three longitudinal regions were corrected for three tests, whereas comparisons between the four circumferential regions were corrected for six possible tests. In some cases, the extent of the change due to age was compared between regions, and the resulting $P$ values have been corrected for three tests for the longitudinal regions or six tests for the circumferential regions. Bonferroni-

inflated $P$ values are stated for each test where applicable, indicated as $P^B$.

An analysis of covariance (ANCOVA) was performed to determine the influence of systolic blood pressure (SBP), diastolic blood pressure (DBP), and the ratio of LV mass to LV end-diastolic volume (EDV) on the rate of relaxation of each strain parameter.

## RESULTS

### *Subjects*

Hemodynamic and global function data for this group have been described elsewhere (37). Briefly, both SBP and DBP were significantly higher in the older group (SBP: 146 ± 15.6 vs. 123.5 ± 14.5 mmHg, $P < 0.0001$; DBP: 83.2 ± 9.92 vs. 65.5 ± 5.54 mmHg, $P < 0.0001$). There were no significant differences in heart rate [70.3 ± 11.3 vs. 69.7 ± 9.8 beats/min, $P$ = not significant (NS)], ejection fraction (69.3 ± 6.6 vs. 70.7 ± 3.0%, $P$ = NS), or LV mass (146 ± 38.7 vs. 143 ± 34.1 g, $P$ = NS) between the older and younger groups, respectively. EDV and stroke volume were significantly smaller in the older group (EDV: 115.7 ± 27.1 vs. 137.5 ± 26.7 ml, $P = 0.031$; stroke volume: 79.8 ± 19.5 vs. 97.1 ± 18.8 ml, $P = 0.018$). The ratio of LV mass to EDV was significantly greater in the older group (1.28 ± 0.3 vs. 1.04 ± 0.1, $P = 0.006$). Taking both groups together, the ratio of LV mass to EDV correlated with both the SBP ($r = 0.610$, $P < 0.001$) and DBP ($r = 0.650$, $P < 0.001$). Transthoracic Doppler echocardiography showed a reduced diastolic peak E velocity and increased peak A velocity in older subjects (E: 46.2 ± 10 vs. 74.2 ± 16.6 m/s, $P < 0.001$; A: 57.9 ± 12.5 vs. 41.3 ± 8.1 m/s, $P < 0.001$). This resulted in a significantly decreased E/A ratio in the older people (0.8 ± 0.2 vs. 1.8 ± 0.3, $P < 0.001$).

### *Peak Systolic Shortening Strain*

The peak value of circumferential percent shortening, $S_C$, was not significantly different between groups globally (20 ± 2.9 older vs. 21.2 ± 1.1% younger, $P$ = NS; Fig. 3, *A* and *B*). $S_C$ was regionally heterogeneous, longitudinally as well as circumferentially ($P < 0.001$ in both directions). The longitudinal variation altered with age ($P = 0.005$ for interaction between region and age). Whereas the apex showed greater peak shortening than the base in both age groups ($P^B < 0.001$ for each group), $S_C$ was reduced only in the apex in the older subjects ($P^B = 0.009$).

Peak longitudinal strain, $S_L$, was not significantly different between groups globally (16.9 ± 2.5 older vs. 18 ± 1.2% younger, $P$ = NS; Fig. 3, *C* and *D*). $S_L$ was regionally heterogeneous, longitudinally as well as circumferentially ($P < 0.001$ in both directions). Aging altered both the longitudinal variation ($P = 0.009$) and the circumferential variation ($P = 0.003$) in $S_L$. The apex showed a greater $S_L$ than the base in the younger

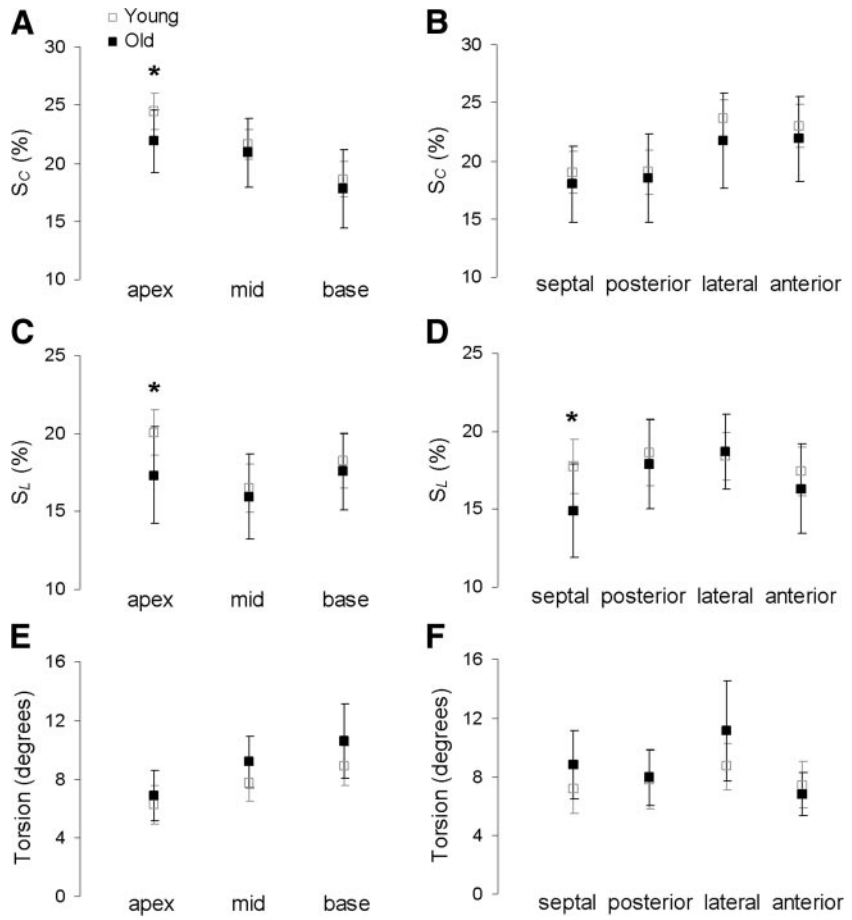


Fig. 3. Peak circumferential ($S_C$) and longitudinal shortening strain ($S_L$) and torsion across the 3 longitudinal regions (*A*, *C*, and *E*, respectively) and across the 4 circumferential regions (*B*, *D*, and *F*, respectively) in old and young subjects. Changes due to age that are significant after Bonferroni correction are indicated for each region (*$P^B < 0.05$).

group ($P^B = 0.018$), but this difference was abolished in the older group ($P$ = NS). The lateral wall showed higher $S_L$ than the septum in the older subjects ($P^B < 0.001$), but this difference was not observed in the younger group ($P$ = NS). $S_L$ was reduced in the older subjects at the apex ($P^B = 0.01$) and the septum ($P^B = 0.01$) only.

Peak torsional shear strain, $S_T$, was increased overall in the older group (9.1 ± 1.7 vs. 7.8 ± 0.9°, $P = 0.017$; Fig. 3, *E* and *F*) and was regionally heterogeneous longitudinally as well as circumferentially ($P < 0.001$ in both directions). The pattern of regional heterogeneity did not change significantly with age ($P$ = NS).

The peak systolic circumferential strain rate was reduced overall in the older group (106.3 ± 14.6 vs. 114.8 ± 6.7%/s, $P = 0.047$) and was regionally heterogeneous both longitudinally and circumferentially ($P < 0.001$). The pattern of regional heterogeneity did not change significantly with age ($P$ = NS).

The peak systolic longitudinal strain rate was reduced overall in the older group (94.5 ± 11.7 vs. 112.8 ± 9.3%/s, $P < 0.001$) and was regionally heterogeneous both longitudinally and circumferentially ($P < 0.001$). However, the pattern of regional heterogeneity did not change significantly with age ($P$ = NS).

The peak rate of change in torsion during systole was not significantly different between groups (65.1 ± 11.7 older vs. 74.3 ± 17.9 degrees/s younger, $P$ = NS) and was regionally heterogeneous both longitudinally ($P < 0.001$) and circumferentially ($P = 0.021$). The pattern of regional heterogeneity did not change significantly with age ($P$ = NS).

### *Peak Rate of Relaxation*

Peak rate of relaxation of circumferential strain, $R_C$, was reduced overall in the older group (104.5 ± 27.7 vs. 162.7 ± 18.2%/s, $P < 0.001$) and was regionally heterogeneous, longitudinally ($P = 0.001$) as well as circumferentially ($P < 0.001$). Aging altered both the longitudinal variation ($P < 0.001$) and the circumferential variation ($P = 0.001$) in $R_C$. A greater $R_C$ was observed in the apex than in the base in younger subjects ($P^B < 0.001$); this difference was not observed in the older subjects, however ($P$ = NS). In both age groups, a greater $R_C$ was observed in the lateral wall than in the septum ($P^B < 0.001$ for each). Significant decreases in $R_C$, due to age, were observed in all regions ($P^B < 0.05$ for each). This decrease in $R_C$ was greater in the apex than in the base ($P^B < 0.001$; Fig. 4*A*) and greater in the lateral wall than in the septum ($P^B = 0.016$; Fig. 4*B*).

Peak rate of relaxation of longitudinal strain, $R_L$, was reduced overall in the older compared with the young group (93.7 ± 26.9 vs. 154.5 ± 18%/s, $P < 0.001$; see Fig. 4, *C* and *D*) and was regionally heterogeneous circumferentially ($P = 0.008$) but not longitudinally ($P$ = NS). The interaction effect of age and regional strains on $R_L$ was significant both longitudinally ($P < 0.001$) and circumferentially ($P = 0.020$). In the younger group, $R_L$ was greater in the apex than in the base ($P^B < 0.001$). In the older group, however, $R_L$ was greater in the base than in the apex ($P^B = 0.024$). In the older group, $R_L$ was significantly greater in the lateral wall than in the septum ($P^B < 0.001$); there was no difference in $R_L$ between septal and lateral regions in the younger group ($P$ = NS), however. $R_L$ was significantly reduced in the older subjects in all regions ($P^B < 0.001$ for each). This reduction was greater in the apex than in the base ($P^B < 0.001$).

Peak rate of relaxation of torsion, $R_T$, was reduced overall in the older group (74.5 ± 16 vs. 91.1 ± 15.5 degrees/s, $P = 0.006$; Fig. 4, *E* and *F*) and was regionally heterogeneous both longitudinally and circumferentially ($P < 0.001$). Aging altered the longitudinal variation ($P = 0.017$). The base of the ventricle showed a greater $R_T$ than the apex in both age groups ($P^B < 0.001$ for both groups). However, the reduction in $R_T$ due to age was significant in the base only ($P^B = 0.015$, leading to a greater reduction in the base than in the apex, $P^B = 0.035$).

Taking both groups together, globally averaged $R_C$, $R_L$, and $R_T$ were inversely correlated with the ratio of LV mass to EDV ($R_C$: $r = 0.758$, $P < 0.001$; $R_L$: $r = 0.742$, $P < 0.001$; $R_T$: $r = 0.500$, $P < 0.01$). In addition, globally averaged $R_C$, $R_L$, and $R_T$ were also inversely correlated with SBP ($R_C$: $r = 0.627$, $P < 0.001$; $R_L$: $r = 0.588$, $P < 0.001$; $R_T$: $r = 0.383$, $P < 0.05$) and with DBP ($R_C$: $r = 0.737$, $P < 0.001$; $R_L$: $r = 0.723$, $P < 0.001$; $R_T$: $r = 0.382$, $P < 0.05$). However, ANCOVA showed that the effect of age (after correction for the ratio of LV mass to EDV, SBP, and DBP as covariates) was still significant on global $R_C$ and $R_L$ ($P < 0.001$ for each) and global $R_T$ ($P < 0.05$).

### *Time from ED to Peak Strain*

The time to $S_C$ was prolonged overall with age (381.3 ± 21.7 vs. 348 ± 17.4 ms, $P < 0.001$; Fig. 5, *A* and *B*) and was regionally heterogeneous both longitudinally and circumferentially ($P < 0.001$). Aging altered both the longitudinal variation ($P < 0.001$) and the circumferential variation ($P = 0.003$) in time to $S_C$. In the younger group, $S_C$ occurred later in the apex than in the base ($P^B < 0.001$); however, in the older group, the peak value was achieved later in the base than in the apex ($P^B = 0.009$). $S_C$ in the lateral wall occurred later than in the septum in younger subjects ($P^B < 0.001$) but not in the older subjects ($P$ = NS). The increase in time to $S_C$ due to age was significant in all regions except the apex and the posterior wall ($P^B < 0.05$ for each).

Similarly, the time to $S_L$ was prolonged overall with age (393.8 ± 36.8 vs. 362.3 ± 23.2 ms, $P = 0.008$; Fig. 5, *C* and *D*) and was regionally heterogeneous both longitudinally ($P = 0.001$) and circumferentially ($P = 0.042$). The longitudinal variation altered with age ($P = 0.002$). $S_L$ was achieved later in the base than in the apex in the older group ($P^B < 0.001$). This difference was not observed in the younger group ($P$ = NS). The increase in time to $S_L$ due to age was significant in

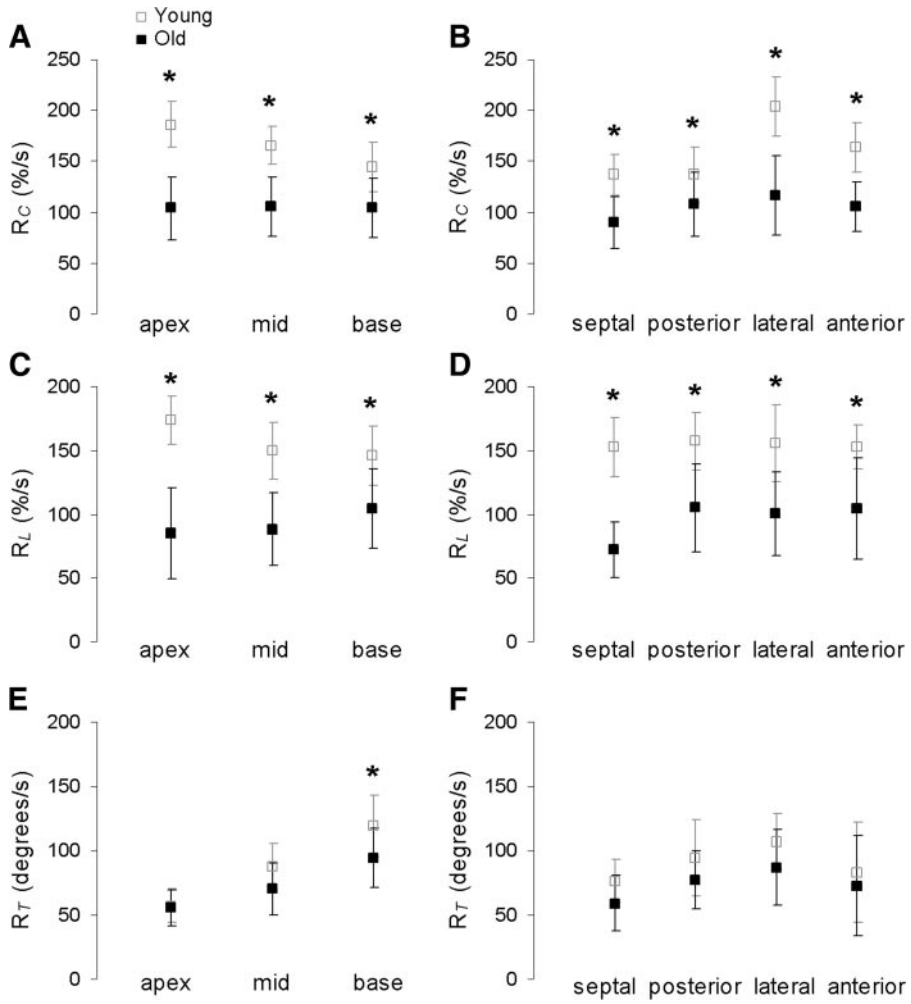


Fig. 4. Peak rate of relaxation of circumferential ($R_C$) and longitudinal shortening strain ($R_L$) and recovery of torsion ($R_T$) across the 3 longitudinal regions (*A*, *C*, and *E*, respectively) and across the 4 circumferential regions (*B*, *D*, and *F*, respectively) in old and young subjects. $*P^B < 0.05$.

the midventricular region ($P^B = 0.023$) and the base ($P^B = 0.004$) only.

Time to peak torsion was unchanged between age groups overall (432.7 ± 62.6 older vs. 425.1 ± 57.7 ms younger, $P$ = NS; see Fig. 5, *E* and *F*) and was regionally heterogeneous longitudinally ($P < 0.001$) but not circumferentially ($P$ = NS). The pattern of regional heterogeneity in time to peak torsion did not alter significantly with age ($P$ = NS).

*Time from ED to Peak Rate of Relaxation*

Time to $R_C$ was increased overall in the older group (522.7 ± 51.9 vs. 482.8 ± 23.9 ms, $P = 0.011$). No significant regional heterogeneity in time to $R_C$ was observed, either along the length of the LV or around the circumference ($P$ = NS for both directions). The interaction effect of age and regional strains on time to $R_C$ was also nonsignificant both longitudinally and circumferentially.

Time to $R_L$ was not different overall between the older and younger groups (525.1 ± 66.5 vs. 497.7 ± 33.7 ms, $P$ = NS). Time to $R_L$ was regionally heterogeneous circumferentially ($P = 0.012$) but not longitudinally ($P$ = NS). Aging did not alter the pattern of regional heterogeneity in time to $R_L$ ($P$ = NS).

Similarly, no significant difference in time to $R_T$ was observed between old and young individuals (478.5 ± 43.8 vs. 471.7 ± 24.8 ms, $P$ = NS). Time to $R_T$ was regionally heterogeneous circumferentially ($P = 0.031$) but not longitudinally ($P$ = NS). Aging did not alter the pattern of regional heterogeneity in time to $R_T$ ($P$ = NS).

The peak rate of relaxation of torsion, over all subjects, was achieved earlier than the peak rate of relaxation of both circumferential ($P^B < 0.001$) and longitudinal ($P^B < 0.001$) strains.

*Asynchrony of Contraction and Relaxation*

In the older subjects, increased regional asynchrony was observed in time to peak circumferential (46.8 ± 11.5 vs. 37.5 ± 7 ms, $P = 0.011$) and longitudinal (60.1 ± 19 vs. 45.7 ± 10.7 ms, $P = 0.015$) shortening strains. Regional asynchrony in time to peak torsion was not different between the older and younger groups (105 ± 42.3 vs. 96.4 ± 49.2 ms, $P$ = NS). The time to $R_C$ was more asynchronous in the older than in the younger group (39.7 ± 12.1 vs. 21.6 ± 4.9 ms, $P < 0.001$). Similarly, increased regional asynchrony in time to $R_L$ was observed in the older group (46.4 ± 15.6 vs. 26.1 ± 7.7 ms, $P < 0.001$). Regional asynchrony in

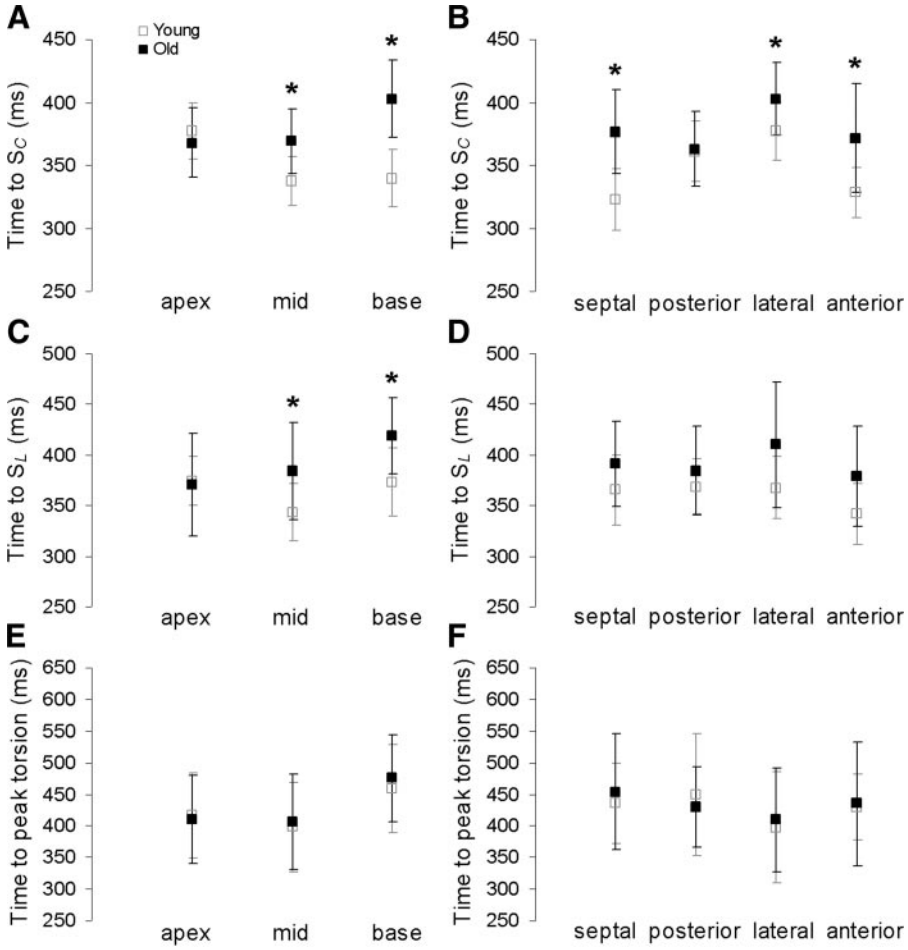


Fig. 5. Time from ED to $S_C$, $S_L$, and peak torsion across the 3 longitudinal regions (*A*, *C*, and *E*, respectively) and across the 4 circumferential regions (*B*, *D*, and *F*, respectively) in old and young subjects. $*P^B < 0.05$.

time to peak rate of relaxation of torsion was not different between old and young groups, however (59 ± 25.3 vs. 51 ± 15.8 ms, $P$ = NS).

## DISCUSSION

It has been well established that cardiac structure and function alter with age (17, 34, 39). Recent studies have shown that the earliest manifestation of these age-related changes is abnormal LV diastolic filling and that diastolic dysfunction is highly prevalent in the elderly population (32, 47). LV filling is influenced by a number of interrelated factors including myocardial relaxation, heart rate, myocardial compliance, atrial function, and filling pressure. The process of LV filling has been studied extensively, and parameters such as the E/A ratio, peak filling rate, filling pressure, and EDV are used routinely in the assessment of diastolic function (3, 30, 35, 43). However, these parameters are more reflective of chamber hemodynamics and blood flow than of myocardial relaxation itself. In the absence of systolic dysfunction, abnormal diastolic function is usually due to abnormal relaxation and/or changes in the passive LV characteristics. Therefore, an understanding of normal relaxation patterns is important in the clinical assessment of diastolic function.

Recently, we have shown that aging causes significant alterations in global LV myocardial relaxation (37). In particular, circumferential and longitudinal shortening persists into diastole in older people, who also experience increased torsion and reduced strain relaxation rates. Because it is likely that impairment in localized portions of the myocardium may underlie the changes observed in global function, and that changes in regional function may be masked by global measures, a study of the influence of age on regional myocardial function is necessary.

Thus, in the present study, we aimed to noninvasively assess the normal changes in regional myocardial relaxation that occur with age, and, in support of the work done by Kuijer et al. (27), we have demonstrated the potential utility of 3-D MR tagging for the quantification of regional LV diastolic function. Our data show that not only are peak LV systolic shortening strain and torsion regionally heterogeneous, as others have shown (5, 19), but peak myocardial relaxation rates are also markedly heterogeneous, and the impairment that occurs with age is similarly nonuniform.

### *Global Function*

LV ejection fraction was preserved in the older subjects, as was LV mass, in agreement with other studies (22, 41). Stroke volume was found to be significantly smaller in older subjects. The ratio of LV mass to EDV

was increased, indicating a mild concentric hypertrophy consistent with the decrease in EDV that was observed in the older group. Both SBP and DBP were higher in the older group, as reported by others (6, 17), and correlated with the ratio of LV mass to EDV, consistent with increasing concentric hypertrophy as blood pressure increases. Echocardiography produced results in accordance with previous studies of diastolic function in the elderly (23, 33, 44, 47) with a reduced E/A value observed in the older subjects.

*Peak Systolic Shortening and Torsion*

The regional heterogeneity in systolic function observed agrees with previous findings (5). On average, peak circumferential and longitudinal shortening in the older group was similar to that observed in younger subjects, in agreement with other studies that have shown that aging causes little change in LV systolic function at rest (1, 6, 14, 17). However, the interaction of age with region was significant, and, on examination of regional differences (after Bonferroni correction), apical shortening was impaired in both circumferential and longitudinal directions and longitudinal shortening was impaired in the septum. Thus regional function parameters may be more sensitive than global parameters for evaluating systolic function.

Peak torsional shear strain was found to be greater in the older group overall, possibly due to an increase in concentric hypertrophy (mass-to-volume ratio), because LV torsion is known to be increased with hypertrophy (45, 55). Though peak torsion was nonuniform along the length of the LV as well as around the circumference, aging did not have any effect on the pattern of this regional heterogeneity.

During systole, the rates of change of both circumferential and longitudinal strains were reduced overall in the older group and were regionally heterogeneous in both the longitudinal and the circumferential directions. Though the systolic rate of change in torsion was, on average, similar in old and young individuals, it was also regionally heterogeneous. However, aging did not influence the pattern of regional nonuniformity in any of the three systolic strain rate parameters.

*Peak Rate of Relaxation*

The peak rate of relaxation of circumferential and longitudinal strains and the peak rate of recovery of torsion were, on average, reduced in older subjects. Age-related decrease in $Ca^{2+}$ uptake by the sarcoplasmic reticulum (40) and an increase in myocardial stiffness (48) may explain in part why myocardial relaxation is slower in these individuals. It is suggested that a reduced relaxation rate is directly related to the diastolic dysfunction observed in the elderly. Our results demonstrate that the process of myocardial relaxation is regionally heterogeneous at all ages. The most dramatic reductions in regional relaxation rate occurred in the apex for circumferential and longitudinal relaxation. This region is also associated with reduced peak systolic strain, although not to as great an extent. Peak systolic strain rates were also slightly reduced overall but showed no change in the pattern of heterogeneity with age. This finding suggests that regional diastolic relaxation parameters may be more sensitive than regional systolic parameters for the detection of impaired function.

Currently, tissue Doppler imaging is commonly used to assess diastolic function (32, 35, 43), giving measures of longitudinal motion and strain rate at the mitral annulus region. Our study shows that longitudinal relaxation is more severely reduced in the apex than in the base and that the lateral wall undergoes greater longitudinal relaxation than the septum in the older group only. An awareness of regional nonuniformity in myocardial strain rate in the longitudinal direction is therefore important in the interpretation of echocardiographic data.

The peak rates of relaxation of both circumferential and longitudinal strains were inversely correlated with the ratio of LV mass to EDV and with SBP and DBP, suggesting that relaxation rates are influenced by concentric hypertrophy and possibly by hypertension. Nevertheless, the ANCOVA (in which the covariate effects of the LV mass-to-EDV ratio, SBP, and DBP were accounted for) showed that hypertrophy or hypertension alone do not explain impairment of global rates of relaxation.

*Time from ED to Peak Shortening and Torsion*

Time from ED to both peak circumferential and peak longitudinal shortening strain was prolonged in the older individuals. This result was unexpected, because others have reported no change in peak ejection rate and time to end systole at rest (12, 23). However, animal studies (28, 46) have shown an age-associated prolongation of the duration of contraction.

*Time from ED to Peak Rate of Relaxation*

The time from ED to peak rate of relaxation of circumferential strain was prolonged with age. This was expected because time to peak filling rate and the time constant of LV pressure decay both increase with age (6, 29, 48). However, time to peak rate of relaxation of longitudinal strain and time to peak rate of recovery of torsion were not different between the two age groups. In support of the findings of Kuijer et al. (27), we found that peak rate of recovery of torsion was achieved earlier than peak rate of relaxation of both circumferential and longitudinal strains, in all subjects. This finding supports the hypothesis that torsion recovery in early diastole may be dependent on the release of stored elastic energy in the myocardium, as well as on LV filling (10, 27).

*Asynchrony*

Our results suggest that regional asynchrony in time to peak circumferential and longitudinal shortening strains, as well as time to peak relaxation rates, increases with age in a fashion that is inconsistent between individuals. Bonow et al. (6) and Furutani et al.

(14) both reported a significant increase in indexes of regional diastolic asynchrony with age, particularly with respect to time to peak filling rate, and showed that this increased asynchrony was inversely correlated with both the rate and extent of global rapid filling.

*Study Limitations and Future Directions*

The temporal resolution that is currently possible with MRI is limited, and this may influence the accuracy of the measurement of peak rate of relaxation and time to peak relaxation. Although better temporal resolution is possible with strain rate echocardiography (20), this technique does not allow measurement of all components of myocardial strain and relaxation and cannot account for through-plane motion effects, as is possible with MRI. It is expected that with the development of faster MR imaging techniques approaching echocardiographic frame rates, it will be possible to obtain more reliable estimates of the extent and temporal evolution of myocardial strains.

We cannot rule out with absolute certainty the presence of coronary artery disease in our subjects because coronary angiography or stress tests were not performed. Thus it is possible that some of the impairment observed in older subjects may be due to undetected cardiovascular disease.

Off-line analysis of cardiac images is still quite labor intensive; however, recent improvements in the field are making the process increasingly automated (2, 16, 26, 36).

In summary, MR tagging is a highly effective tool for the description and quantification of local as well as global changes in myocardial function. Our results show that marked regional nonuniformities in myocardial relaxation exist in both old and young people and that changes in the nonuniform pattern of myocardial contraction and relaxation occur with age. This has important implications for cardiovascular disease and highlights the importance of taking into account the normal age-related changes in myocardial function in studies of disease.

## DISCLOSURES

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## REFERENCES

1. **Abu-Erreish G, Neely J, Whitmer J, Whitman V, and Sanadi D.** Fatty acid oxidation by isolated perfused working hearts of aged rats. *Am J Physiol Endocrinol Metab Gastrointest Physiol* 232: E258–E262, 1977.
2. **Aletras A, Balaban R, and Wen H.** High-resolution strain analysis of the human heart with fast-DENSE. *J Magn Reson* 140: 41–57, 1999.
3. **Appleton C, Hatle L, and Popp R.** Relation of transmitral flow velocity patterns to left ventricular diastolic function: new insights from a combined hemodynamic and Doppler echocardiographic study. *J Am Coll Cardiol* 12: 426–440, 1988.
4. **Axel L and Dougherty L.** MR imaging of motion with spatial modulation of magnetization. *Radiology* 171: 841–845, 1989.
5. **Bogaert J and Rademakers F.** Regional nonuniformity of normal adult human left ventricle. *Am J Physiol Heart Circ Physiol* 280: H610–H620, 2001.
6. **Bonow R, Vitale D, Bacharach S, Maron B, and Green M.** Effects of aging on asynchronous left ventricular regional function and global ventricular filling in normal human subjects. *J Am Coll Cardiol* 11: 50–58, 1988.
7. **Brutsaert D.** Nonuniformity: a physiologic modulator of contraction and relaxation of the normal heart. *J Am Coll Cardiol* 9: 341–348, 1987.
8. **Cacciapuoti F, D'Avino M, Lama D, Bianchi U, Perrone N, and Varricchio M.** Progressive impairment of left ventricular diastolic filling with advancing age: a Doppler echocardiographic study. *J Am Geriatr Soc* 40: 245–250, 1992.
9. **D'hooge J, Heimdal A, Jamal F, Kukulski T, Bijnens B, Rademakers F, Hatle L, Suetens P, and Sutherland G.** Regional strain and strain rate measurements by cardiac ultrasound: principles, implementation and limitations. *Eur J Echocardiogr* 1: 154–170, 2000.
10. **Dong S, Hees P, Siu C, Weiss J, and Shapiro E.** MRI assessment of LV relaxation by untwisting rate: a new isovolumic phase measure of tau. *Am J Physiol Heart Circ Physiol* 281: H2002–H2009, 2001.
11. **Edvardsen T, Gerber B, Garot J, Bluemke D, Lima J, and Smiseth O.** Quantitative assessment of intrinsic regional myocardial deformation by Doppler strain rate echocardiography in humans: validation against three-dimensional tagged magnetic resonance imaging. *Circulation* 106: 50–56, 2002.
12. **Fioranelli M, Piccoli M, Mileto G, Risa M, Sgreccia F, Azzolini A, and Puglisi A.** Modifications in cardiovascular functional parameters with aging. *Minerva Cardioangiol* 49: 169–178, 2001.
13. **Fung Y.** *Foundations of Solid Mechanics.* Englewood Cliffs, NJ: Prentice-Hall, 1965.
14. **Furutani Y, Yuki K, Yamada H, Yano M, Yamagishi T, Ozaki M, and Kusukawa R.** Age-related modification of regional left ventricular filling in normal subjects. *Jpn Circ J* 57: 312–321, 1993.
15. **Garcia-Fernandez M, Azevedo J, Moreno M, Bermejo J, Perez-Castellano N, Puerta P, Desco M, Antoranz C, Serrano J, Garcia E, and Delcan J.** Regional diastolic function in ischaemic heart disease using pulsed wave Doppler tissue imaging. *Eur Heart J* 20: 496–505, 1999.
16. **Garot J, Bluemke D, Osman N, Rochitte C, McVeigh E, Zerhouni E, Prince J, and Lima J.** Fast determination of regional myocardial strain fields from tagged cardiac images using harmonic phase MRI. *Circulation* 101: 981–988, 2000.
17. **Gerstenblith G, Frederiksen J, Yin F, Fortuin N, Lakatta E, and Weisfeldt M.** Echocardiographic assessment of a normal adult aging population. *Circulation* 56: 273–278, 1977.
18. **Greenbaum R and Gibson D.** Regional non-uniformity of left ventricular wall movement in man. *Br Heart J* 45: 29–34, 1981.
19. **Hansen D, Daughters G 2nd, Alderman E, Ingels N Jr, and Miller D.** Torsional deformation of the left ventricular midwall in human hearts with intramyocardial markers: regional heterogeneity and sensitivity to the inotropic effects of abrupt rate changes. *Circ Res* 62: 941–952, 1988.
20. **Heimdal A, Stoylen A, Torp H, and Skjaerpe T.** Real-time strain rate imaging of the left ventricle by ultrasound. *J Am Soc Echocardiogr* 11: 1013–1019, 1998.
21. **Hoffmann R, Altiok E, Nowak B, Heussen N, Kuhl H, Kaiser H, Bull U, and Hanrath P.** Strain rate measurement by doppler echocardiography allows improved assessment of myocardial viability in patients with depressed left ventricular function. *J Am Coll Cardiol* 39: 443–449, 2002.
22. **Kitzman D, Scholz D, Hagen P, Ilstrup D, and Edwards W.** Age-related changes in normal human hearts during the first 10 decades of life. Part II (maturity): a quantitative anatomic study of 765 specimens from subjects 20 to 99 years old. *Mayo Clin Proc* 63: 137–146, 1988.
23. **Kitzman D, Sheikh K, Beere P, Philips J, and Higginbotham M.** Age-related alterations of Doppler left ventricular filling indexes in normal subjects are independent of left ventricular mass, heart rate, contractility and loading conditions. *J Am Coll Cardiol* 18: 1243–1250, 1991.
24. **Klein A, Burstow D, Tajik A, Zachariah P, Bailey K, and Seward J.** Effects of age on left ventricular dimensions and

filling dynamics in 117 normal persons. *Mayo Clin Proc* 69: 212–224, 1994.
25. **Kramer C, Reichek N, Ferrari V, Theobald T, Dawson J, and Axel L.** Regional heterogeneity of function in hypertrophic cardiomyopathy. *Circulation* 90: 186–194, 1994.
26. **Kuijer J, Jansen E, Marcus J, van Rossum A, and Heethaar R.** Improved harmonic phase myocardial strain maps. *Magn Reson Med* 46: 993–999, 2001.
27. **Kuijer J, Marcus J, Gotte M, van Rossum A, and Heethaar R.** Three-dimensional myocardial strains at end-systole and during diastole in the left ventricle of normal humans. *J Cardiovasc Magn Reson* 4: 341–351, 2002.
28. **Lakatta E, Gerstenblith G, Angell C, Shock N, and Weisfeldt M.** Prolonged contraction duration in aged myocardium. *J Clin Invest* 55: 61–68, 1975.
29. **Lakatta E, Mitchell J, Pomerance A, and Rowe G.** Human aging: changes in structure and function. *J Am Coll Cardiol* 10: 42A–47A, 1987.
30. **Little W and Downes T.** Clinical evaluation of left ventricular diastolic performance. *Prog Cardiovasc Dis* 32: 273–290, 1990.
31. **Maier S, Fischer S, McKinnon G, Hess O, Krayenbuehl H, and Boesiger P.** Evaluation of left ventricular segmental wall motion in hypertrophic cardiomyopathy with myocardial tagging. *Circulation* 86: 1919–1928, 1992.
32. **Mandinov L, Eberli F, Seiler C, and Hess O.** Diastolic heart failure. *Cardiovasc Res* 45: 813–825, 2000.
33. **Mantero A, Gentile F, Gualtierotti C, Azzollini M, Barbier P, Beretta L, Casazza F, Corno R, Giagnoni E, Lippolis A, Lombroso S, Mattioli R, Morabito A, Ornaghi M, Pepi M, and Pezzano A.** Left ventricular diastolic parameters in 288 normal subjects from 20 to 80 years old. *Eur Heart J* 16: 94–105, 1995.
34. **Miller T, Grossman S, Schectman K, Biello D, Ludbrook P, and Ehsani A.** Left ventricular diastolic filling and its association with age. *Am J Cardiol* 58: 531–535, 1986.
35. **Nagueh S, Middleton K, Spencer W, Zoghbi W, and Quinones M.** Doppler estimation of left ventricular filling pressure in patients with hypertrophic cardiomyopathy. *Circulation* 99: 254–261, 1999.
36. **Osman N, Kerwin W, McVeigh E, and Prince J.** Cardiac motion tracking using CINE harmonic phase (HARP) magnetic resonance imaging. *Magn Reson Med* 42: 1048–1060, 1999.
37. **Oxenham H, Young A, Cowan B, Gentles T, Occleshaw C, Fonseca C, Doughty R, and Sharpe N.** Age-related changes in myocardial relaxation using three-dimensional tagged magnetic resonance imaging. *J Cardiovasc Magn Reson*. In press.
38. **Paelinck B, Lamb H, Bax J, Van der Wall E, and de Roos A.** Assessment of diastolic function by cardiovascular magnetic resonance. *Am Heart J* 144: 198–205, 2002.
39. **Patel M and Sonnenblick E.** Age associated alterations in structure and function of the cardiovascular system. *Am J Geriatr Cardiol* 7: 15–22, 1998.
40. **Pugh K and Wei J.** Clinical implications of physiological changes in the aging heart. *Drugs Aging* 18: 263–276, 2001.
41. **Sandstede J, Lipke C, Beer M, Hofmann S, Pabst T, Kenn W, Neubauer S, and Hahn D.** Age- and gender-specific differences in left and right ventricular cardiac function and mass determined by cine magnetic resonance imaging. *Eur Radiol* 10: 438–442, 2000.
42. **Schiller N, Shah P, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I, Silverman N, and Tajik A.** Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 2: 358–367, 1989.
43. **Sohn D, Chai I, Lee D, Kim H, Kim H, Oh B, Lee M, Park Y, Choi Y, Seo J, and Lee Y.** Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. *J Am Coll Cardiol* 30: 474–480, 1997.
44. **Spirito P and Maron B.** Influence of aging on Doppler echocardiographic indices of left ventricular diastolic function. *Br Heart J* 59: 672–679, 1988.
45. **Stuber M, Scheidegger M, Fischer S, Nagel E, Steinemann F, Hess O, and Boesiger P.** Alterations in the local myocardial motion pattern in patients suffering from pressure overload due to aortic stenosis. *Circulation* 100: 361–368, 1999.
46. **Templeton G, Platt M, Willerson J, and Weisfeldt M.** Influence of aging on left ventricular hemodynamics and stiffness in beagles. *Circ Res* 44: 189–194, 1979.
47. **Tokushima T, Reid C, and Gardin J.** Left ventricular diastolic function in the elderly. *Am J Geriatr Cardiol* 10: 20–29, 2001.
48. **Villari B, Vassalli G, Schneider J, Chiariello M, and Hess O.** Age dependency of left ventricular diastolic function in pressure overload hypertrophy. *J Am Coll Cardiol* 29: 181–186, 1997.
49. **Wilkenshoff U, Hatle L, Sovany A, Wranne B, and Sutherland G.** Age-dependent changes in regional diastolic function evaluated by color Doppler myocardial imaging: a comparison with pulsed Doppler indexes of global function. *J Am Soc Echocardiogr* 14: 959–969, 2001.
50. **Yamagishi T, Ozaki M, Kumada T, Ikezono T, Shimizu T, Furutani Y, Yamaoka H, Ogawa H, Matsuzaki M, Matsuda Y, Arima A, and Kusukawa R.** Asynchronous left ventricular diastolic filling in patients with isolated disease of the left anterior descending coronary artery: assessment with radionuclide ventriculography. *Circulation* 69: 933–942, 1984.
51. **Young A, Cowan B, Occleshaw C, Oxenham H, and Gentles T.** Temporal evolution of left ventricular strain late after repair of coarctation of the aorta using 3D MR tissue tagging. *J Cardiovasc Magn Reson* 4: 233–243, 2002.
52. **Young A, Cowan B, Thrupp S, Hedley W, and Dell'Italia L.** Left ventricular mass and volume: fast calculation with guidepoint modeling on MR images. *Radiology* 216: 597–602, 2000.
53. **Young A, Imai H, Chang C, and Axel L.** Two-dimensional left ventricular deformation during systole using magnetic resonance imaging with spatial modulation of magnetization. *Circulation* 89: 740–752, 1994.
54. **Young A, Kraitchman D, Dougherty L, and Axel L.** Tracking and finite element analysis of stripe deformation in magnetic resonance tagging. *IEEE Trans Med Imaging* 14: 413–421, 1995.
55. **Young A, Kramer C, Ferrari V, Axel L, and Reichek N.** Three-dimensional left ventricular deformation in hypertrophic cardiomyopathy. *Circulation* 90: 854–867, 1994.
56. **Zerhouni E, Parish D, Rogers W, Yang A, and Shapiro E.** Human heart: tagging with MR imaging–a method for noninvasive assessment of myocardial motion. *Radiology* 169: 59–63, 1988.