Late systolic onset of regional LV relaxation demonstrated in three-dimensional space by MRI tissue tagging

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Late systolic onset of regional LV relaxation demonstrated in three-dimensional space by MRI tissue tagging. Am J Physiol Heart Circ Physiol 287: H1740–H1746, 2004. First published June 17, 2004; 10.1152/ajpheart.00080.2004.—Left ventricular (LV) relaxation entails myocardial deformation that induces LV filling. Yet, the precise mechanisms of the earliest changes in tissue properties that characterize myocardial relaxation remain incompletely understood. Ten healthy volunteers (seven males, 25–43 yr, underwent tagged and cine MRI with high temporal resolution (25–35 ms). Normal strains including radial (E_r), circumferential (E_c), and longitudinal (E_l) strains, shear strains including E_s (circumferential-longitudinal), E_cr (circumferential-radial), and E_cl (radial-longitudinal), and principal strains (E_1, E_2, and E_3) were calculated using a displacement field-fitting method. Temporal changes in angular strains indicative of shear and torsion release and normal strains were studied during late systole and early relaxation. The onset of individual relaxation strains was heterogeneous relative to LV filling. Shear strains (E_s, E_cr, and E_cl) and radial thinning were first to develop. Times of onset of E_r, E_c, and E_l occurred 108, 93, 67, and 73 ms before aortic valve closure, respectively. E_l, E_cr, and LV volume change commenced significantly later after the onset of diastolic shear strains and radial thinning. The onset of E_c, E_l, and LV volume change was noted 38 ms before aortic valve closure (P ≤ 0.05 relative to the onset of shear strains and E_l). Myocardial relaxation is characterized by a three-dimensional unfolding deformation that includes release of torsion, shear, and radial thinning beginning before aortic valve closure. This unfolding pattern precedes longitudinal and circumferential elongation and may facilitate early diastolic filling.

ABNORMAL MYOCARDIAL RELAXATION plays an important role in the pathogenesis of common disorders, including congestive heart failure accompanied by left ventricular (LV) hypertrophy, cardiomyopathies, and valvular diseases (19, 26, 28). However, the full scope of events underlying the onset of myocardial relaxation remains incompletely understood.

It is well established that myocardial displacement during the early stages of relaxation induces LV filling, and that such an activity, which can be expressed in terms of strain changes, plays a central role in myocardial diastolic function. Mitral valve opening is driven by the left atrial (LA)-LV pressure gradient generated by LA filling and LV relaxation. Previous studies demonstrated that ventricular relaxation commences during the ejection period, and the factors affecting its control have also been described previously (4, 23, 25).

Myocardial relaxation is an active process initiated by the Ca^{2+} reuptake by the sarcoplasmic reticulum. The release of elastic energy stored during systole in the myocardial fibers, in the elastic elements, and in the extracellular matrix augments the process of relaxation. This process is mediated by a unique angular motion termed untwisting (2, 20, 22).

LV untwisting reflects only one part of the consequences of shear strains. Moreover, neither the onset of myocardial relaxation nor the events that characterize the return of the LV to its preceding state in end diastole have been fully elucidated in three-dimensional (3-D) space. Such insight is crucial to a better understanding of the complex 3-D myocardial relaxation process that precedes LV filling and how diastole is triggered in the normal human heart.

Cardiac MRI with myocardial tagging (27) enables tracking of the various components of cardiac deformation throughout the cardiac cycle. 3-D systolic deformation of the heart has been characterized in detail by MRI with tissue tagging (16, 18).

The purpose of this study was to analyze in detail the process of myocardial displacement relative to LV relaxation in the normal human heart. Our aim was to determine the detailed time sequence of LV relaxation in 3-D space as changes in shear and normal strains during late systole and the earliest stages of myocardial relaxation. We focused specifically on the onset of 3-D changes in the angular deformations that represent the release of shear forces inducing myocardial relaxation.

METHODS

Ten adult volunteers with no apparent cardiac disease (seven males and three females), 25–43 yr of age, underwent tagged MRI. Their heart rate was 67 ± 12 beats/min (mean ± SD), and the range was 54–85 beats/min. All the participants gave informed consent for the study protocol, which was approved by the Johns Hopkins Hospital Institutional Review Board.

Images were acquired on a whole body magnet (1.5T CVI, General Electric Medical Systems; Waukesha, WI). A four-channel phased array surface coil was used for signal reception. After acquisition of axial and oblique scout images, six short-axis slices (apex to base), with striped tags obtained separately in two orthogonal orientations, and six radial long-axis slices were acquired every 30° using an ECG-triggered fast gradient echo pulse sequence with spatial modulation of magnetization (SPAMM). Images were acquired during ~20-s breath holds. A tagged cardiac image is shown in Fig. 1.

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compared with LV volume curves analyzed by a displacement changes in normal and shear strains were plotted over time and lar, and basal slices in the epicardium, midwall, and endocardium. The torsion release). All six strains were computed in apical, midventricular and circumferential direction) is an indicator of torsion (and tissue is deformed to a parallelepiped.

By virtue of the normal and shear strains, a cube of myocardial 2 myocardial tissue without bulk translation or rotations is shown in Fig. 1. Myocardial tagging. A and B: diastolic frames of short-axis slices with vertical and horizontal tags in the plane of the papillary muscles. C: long-axis slice (four-chamber view). D–F: systolic frames. The illustrated white lines indicate the location of the tags, endocardial and epicardial contours. Note the deformation of the tag points during systole.

Imaging parameters were the following: field of view 36 cm; slice thickness 8 mm; tag spacing of 7 mm; slice gap 4–5 mm; repetition time 5.5 ms; echo time 2 ms; flip angle 15°; matrix size 256 × 128; 4–6 phase encoding views per segment; and bandwidth 62.5 kHz. The temporal resolution in the tagged series was 22–35 ms.

Data analysis. Tags were tracked with the use of the FINDTAGS software; 3-D strains were analyzed by a displacement field-fitting program as described previously (10, 18).

Strain is defined by the formula

\[ \text{Strain} = \frac{(L_d - L_s)}{L_s} \]

where \( L_d \) is the length in the deformed state and \( L_s \) is the length in the relaxed state (end diastole).

We computed three normal strains (Fig. 2A), including radial thickening/thinning (\( E_r \)) and circumferential (\( E_\phi \)) and longitudinal (\( E_l \)) shortening/elongation, as well as three shear strains: \( E_{rs} \) (shear in the radial and circumferential plane), \( E_{rl} \) (shear in the circumferential and longitudinal plane), and \( E_{ll} \) (shear in the radial and longitudinal). With the use of this reference, whereas \( E_{rl} \) is an index of shear in the commonly obtained short-axis plane, \( E_{rl} \) (shear between the longitudinal and circumferential direction) is an indicator of torsion (and torsion release). All six strains were computed in apical, midventricular, and basal slices in the epicardium, midwall, and endocardium. The changes in normal and shear strains were plotted over time and compared with LV volume curves analyzed by a displacement field-fitting method. Midwall, midventricular strains are reported unless mentioned otherwise. An illustration showing the deformation of myocardial tissue without bulk translation or rotations is shown in Fig. 2B. By virtue of the normal and shear strains, a cube of myocardial tissue is deformed to a parallelepiped.

Principal strains including \( E_1 \) (maximal thickening/thinning), \( E_2 \) (maximal shortening/lengthening close to the horizontal plane), and \( E_3 \) (maximal shortening/elongation in the circumferential/longitudinal plane) were measured in all volunteers.

The onset of diastolic relaxation of strains (time to breakpoint) was determined as the time from R wave to the time of the development of diastolic strains. The beginning of relaxation was defined by a change in the trend of the first derivative of the particular strain with respect to time, as shown in Fig. 3. Time derivative of the strain is the strain rate (1/s).

In addition, LV torsion was defined as difference between basal and apical rotation angle about the central long axis for each circumferential region divided by the distance between corresponding slices (degrees/cm), and maximal untwisting rate (degrees/s) were calculated using field-fitting displacement mesh. Both parameters were calculated in the midwall layer and reflect an average value for all circumferential regions.

Long-axis tagged images were used to determine times of aortic valve closure (AVC) and mitral valve opening (MVO). Times of AVC and MVO were studied in all subjects, and the times of onset of diastolic strains and volume change were studied in relation to AVC and MVO.

Statistical analysis. Data are presented as means ± SD. One-way ANOVA with repeated measures (STATA-7 software; College Station, TX) was used to compare times of strain onset. Individual comparisons were made post hoc using Bonferroni tests. Statistical significance was defined as \( P \leq 0.05 \).

RESULTS

Temporal course of strain changes relative to aortic valve closure. The time course of measured strain components throughout the cardiac cycle in the normal human heart is displayed in Figs. 3 and 4. The breakpoint time is seen 40 ms before aortic valve closure. The time gap between the bars demonstrating aortic valve closure and mitral valve opening indicates isovolumetric relaxation period, which spans 60 ms. Peak midwall systolic strains in the different levels (base, midventricle, and apex) are shown in Table 1. Peak systolic torsion angle at the midwall layer was 1.6 ± 0.4 degrees/cm, and peak apical untwisting rate was −50.2 ± 9.4 degrees/s.
Table 2 and Fig. 5 show the times of onset of the different strain components associated with myocardial relaxation in relation to aortic valve closure and mitral valve opening. The onset of shear strains associated with relaxation and radial thinning occurred in late systole, ~70–100 ms before the aortic valve closure. The onsets of $E_{cc}$ and $E_{ll}$ were seen 38 ms before aortic valve closure (times of onset of $E_{cc}$ and $E_{ll}$ vs. AVC, $P < 0.05$).

Temporal course of strain changes relative to previous end diastole. The times of onset of reversal of midwall, midventricular diastolic shear strains $E_{cr}$, $E_{cl}$, and $E_{cl}$, respectively, were 241 ± 34, 256 ± 27, and 282 ± 31 ms after the previous end diastole (defined by the prior R wave), respectively. As indicated above, radial thinning occurred close to the time of development of shear strains (276 ± 30 ms). The times of onset of $E_{cc}$, $E_{ll}$, and volume increase were 311 ms from the previous end diastole. The time points for $E_{cc}$, $E_{ll}$, and LV volume change were significantly delayed compared with the onset of shear strains and radial thinning in the apical, midventricular, and basal levels ($P < 0.05$).

LV motion along the entire cardiac cycle and during diastole is shown in a cine MRI animation provided online at http://ajpheart.physiology.org/cgi/content/full/00080.2004/DC1. Early reversal of torsion (or untwisting), occurring before increase in circumference and LV volume, can be noticed in this animation.

**Fig. 2.** A: directions of strains. Radial ($E_{rr}$), circumferential ($E_{cc}$), longitudinal ($E_{ll}$), and shear strains: circumferential-longitudinal ($E_{cl}$), circumferential-radial ($E_{cr}$), radial-longitudinal ($E_{rl}$). B: systolic deformation of the myocardial tissue. Illustration of three-dimensional (3-D) strains and their effect on myocardial deformation. For clarity, the effect of each type of strain is shown separately, and the effect of normal strains is presented before shear strains. As a result, the myocardial tissue (cube in end diastole, top, left) is deformed to a parallelepiped configuration (middle, right).
thinning and shear strains, $P < 0.05$). The time point of LV volume increase occurred slightly before the time of aortic valve closure (38 ms, $P < 0.05$) followed by a plateau with minimal volume changes (Fig. 4), until mitral valve opening to the end of diastole. Time (in ms) is determined from previous end diastole (peak R wave). The strain plots were obtained from basal region (epicardial layer) in one of the participants.

**Evolution of principal strains.** The onset of myocardial relaxation as measured by principal strains ($E_I$ and $E_II$) occurred at approximately the same time as the onset of shear strains ($E_{II}$ and $E_{III}$) and radial thinning ($P$ = not significant). Onset of $E_III$ occurred close to the onset $E_{cc}$ and $E_{II}$ (Table 2).

**Spatial heterogeneity of LV relaxation.** The change in magnitude of the strains, which is associated with diastolic relaxation, tended to occur first in the basal level. However, the time differences between the slices were small (10–25 ms) and were not statistically significant (Table 2). Regarding transmural differences, all strains tended to be begin earlier in the endocardium than the epicardium. Again, time differences were too small (5–15 ms) and not statistically significant. LV relaxation was observed first in the shear strains and radial strain, followed by $E_{III}$, $E_{cc}$, and volume increase in all the slices and layers.

**DISCUSSION**

Detailed insight into myocardial relaxation mechanics is pivotal for a more fundamental understanding of the complex processes that trigger diastole. By utilizing the MRI tagging technique with high temporal resolution, we were able to characterize in detail the onset of regional myocardial tissue displacement and deformation during early relaxation in 3-D space. We report, for the first time in humans, that myocardial displacement associated with LV relaxation starts during late systole. The first event was the development of shear strains, followed by radial thinning, and then the onset of longitudinal and circumferential lengthening ($E_{III}$ and $E_{cc}$). LV longitudinal and circumferential lengthening occurred simultaneously with LV volume increase, ~40 ms after radial thinning and before aortic valve closure. The early occurrence of torsion release (associated with change in $E_{III}$), before increase in circumference (related to $E_{cc}$) and LV volume change, is presented in a kinetic model shown as cine animation provided as previously mentioned in RESULTS.

Several experimental studies in animals have demonstrated evidence that the onset of myocardial relaxation occurs during systole. Solomon et al. (23) showed that the onset of LV relaxation during normal ejection occurred during mid-systole. They demonstrated that the beginning of relaxation occurred soon after the beginning of ejection. With the use of ra-

**Table 1. Peak midwall systolic strain in basal, midcavity, and apical slices**

<table>
<thead>
<tr>
<th>Strain</th>
<th>Basal Slice</th>
<th>Midcavity Slice</th>
<th>Apical Slice</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{rr}$</td>
<td>24.6 ± 13.2</td>
<td>21.9 ± 10.7</td>
<td>25.7 ± 16.9</td>
</tr>
<tr>
<td>$E_{II}$</td>
<td>21.7 ± 8.3</td>
<td>19.5 ± 11.2</td>
<td>23.2 ± 9.8</td>
</tr>
<tr>
<td>$E_{cc}$</td>
<td>22.0 ± 7.4</td>
<td>21.5 ± 9.6</td>
<td>23.5 ± 11.2</td>
</tr>
<tr>
<td>$E_{rr}$</td>
<td>3.6 ± 1.8</td>
<td>3.3 ± 1.5</td>
<td>3.9 ± 2.1</td>
</tr>
<tr>
<td>$E_{II}$</td>
<td>2.6 ± 1.8</td>
<td>2.4 ± 1.6</td>
<td>3.0 ± 2.1</td>
</tr>
<tr>
<td>$E_{cc}$</td>
<td>1.4 ± 0.4</td>
<td>1.2 ± 0.3</td>
<td>1.8 ± 0.5</td>
</tr>
</tbody>
</table>

Values are means ± SD (in %). $E_{rr}$, radial strain; $E_{II}$, longitudinal strain; $E_{cc}$, circumferential strain; $E_{rr}$, circumferential-radial shear strain; $E_{II}$, radial, longitudinal shear strain; $E_{cc}$, circumferential-longitudinal shear strain. Apical peak systolic strains (absolute values) tend to be higher than the basal strains; however, differences between slices were not significant.
normal strains. However, in that study, strains were analyzed before the occurrence of LV torque. They reported changes in LV torque before the increase in circumferential strain. (20) found that untwisting occurred mainly during the isovolumetric relaxation period. With the use of a simulation of an incompressible cylindrical model, it has been demonstrated that torsion is a mechanism whereby transmural stress gradients in the LV are reduced (9, 15).

The time sequence of strain development in myocardial relaxation is determined in part by the fiber orientation and the sequence of electrical activation and repolarization.

The arrangement of myocardial fibers along the LV is complex. Epicardial fibers are arranged in a counter-clockwise spiral from apex to base, whereas endocardial fibers are arranged in the opposite direction (8). Moreover, the orientation of the laminar sheets, which includes the myocardial fibers, coincides with the maximal shear strains during systole (1).

Rademakers et al. (21) studied the contribution of fiber and cross-fiber shortening to the degree of radial thickening during systole in the epicardium and endocardium with tagged MRI. They found that cross-fiber shortening in the endocardium exceeds cross-fiber shortening in the epicardium and fiber shortening at both sites. Cross-fiber shortening was attributed to interactions between the endocardium and epicardium leading to ventricular systolic folding. Our study describes the continuation of this process into the early stages of cross-fiber relaxation leading to reversal of shear strain changes that lead to the onset of radial thinning.

As a result of the complex fiber arrangement and repolarization sequence, this 3-D process of relaxation entails not only untwisting but also release of shear between the epicardial and endocardial layers that is followed by the radial thinning shortly thereafter. We used the term myocardial unfolding to describe this 3-D sequence of events, which include the reversal of shear strains and radial thinning. This unfolding causes the rapid reduction of LV pressure that induces mitral valve opening and the changes in longitudinal and circumferential strains that accompany LV filling.

The onset of a small increase in LV volume before mitral valve opening may reflect a downward motion of the mitral valve plane toward the LV apex caused by a reduction in LV pressure. This early diastolic downward motion of the mitral plane before its opening has been demonstrated previously in echocardiographic studies (7, 12). This initial volume change was very small compared with the later LV filling that follows.

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### Table 2. Time of onset of different types of diastolic strains in different ventricular levels

<table>
<thead>
<tr>
<th>Strain</th>
<th>Basal Slice</th>
<th>Midcavity Slice</th>
<th>Apical Slice</th>
</tr>
</thead>
<tbody>
<tr>
<td>( E_{rc} )</td>
<td>239±38a</td>
<td>241±34d</td>
<td>250±38e</td>
</tr>
<tr>
<td>( E_{rl} )</td>
<td>251±61b</td>
<td>256±27d</td>
<td>275±43</td>
</tr>
<tr>
<td>( E_{rr} )</td>
<td>278±22c</td>
<td>276±30e</td>
<td>302±29</td>
</tr>
<tr>
<td>( E_{cc} )</td>
<td>284±38f</td>
<td>282±31f</td>
<td>287±47</td>
</tr>
<tr>
<td>( E_{cl} )</td>
<td>280±26</td>
<td>288±29</td>
<td>305±39</td>
</tr>
<tr>
<td>( E_{cl} )</td>
<td>300±26</td>
<td>301±32</td>
<td>290±34</td>
</tr>
<tr>
<td>( E_{cc} )</td>
<td>305±27</td>
<td>311±27</td>
<td>323±28</td>
</tr>
<tr>
<td>( E_{ec} )</td>
<td>317±26</td>
<td>311±18</td>
<td>321±29b</td>
</tr>
<tr>
<td>Volume</td>
<td>311±21</td>
<td>311±21</td>
<td>311±21</td>
</tr>
<tr>
<td>AVC</td>
<td>349±33</td>
<td>349±33</td>
<td>349±33b</td>
</tr>
<tr>
<td>MVO</td>
<td>410±35</td>
<td>410±35</td>
<td>410±35</td>
</tr>
</tbody>
</table>

Values are means ± SD (in ms). Average onset of diastolic relaxation of midwall strains (time to breakpoint) determined as the time (ms) from R wave to the time of the development of diastolic strains. The onset of volume change (Volume), aortic valve closure (AVC), and mitral valve opening (MVO) are also shown. Base: *Erc vs. Er, Ecc, and volume, P < 0.01; bEr vs. Ecc, Er, and volume, P < 0.05; cEr vs. Ecc, Er, and volume, P < 0.05. Midventricle: *Erc and Er vs. Ecc, Er, and volume, P < 0.01; *Er vs. Ecc, and volume, P < 0.05; eErc and Er vs. Ecc, and volume, P < 0.01; fEr vs. Ecc, and volume, P < 0.05; Apex: *Erc vs. volume and Ecc, P < 0.01; fEcc, Ecc, Er, and Ecc, P < 0.05; AVC vs. volume, P < 0.05.

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![Fig. 5. Time to development of diastolic midwall strains in the midventricular levels, determined by time to break point. Time to break point describes the time of onset of the various strains. AoVC, aortic valve closure; Ecc, circumferential strain; Vol, volume change; MVO, mitral valve opening. Bar indicates standard deviation. Time is shown in milliseconds. *Erc vs. Er, Ecc, and Vol, P < 0.01; †Erc vs. Ecc, Er, and Ecc, P < 0.05; ‡AVC vs. Vol, P < 0.05.](http://ajpheart.physiology.org/Downloaded-from-http://ajpheart.physiology.org/)

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mitral valve opening as shown in Fig. 4. It is important to note, however, that this time (38 ms) difference between MVO and LV volume change approaches the limits of current temporal resolution employed in our MRI study.

Methodological considerations. The information from each study showed similar patterns that enabled us to depict the timing of late systolic and early diastolic deformation despite a relatively small number of study participants. In all study participants, the onset of relaxation as noted by the different strain components preceded aortic valve closure.

The participants in the present study were normotensive, healthy adults, with no risk factors for coronary artery disease. The magnitudes of their peak systolic strains, torsion angles, and peak untwisting rates fall in the normal range as described in previous studies (11, 14, 16, 24). In a previous study (6), elderly (60–74 yr) individuals were found to have increased regional asynchrony, slower peak relaxation rates, and a longer time to peak relaxation. However, the pattern of relaxation, earlier peak torsion recovery, and only later, circumferential and longitudinal relaxation were similar to our study although they did not measure the times of their onset as was performed in the present normal volunteer study.

The temporal resolution obtained in this MRI study was high (25–35 ms) and enabled a detailed insight into myocardial diastolic properties. This allowed us to evaluate regional myocardial deformation in 3-D, a task that cannot be performed yet by any other imaging modality. Whereas our temporal resolution was high, uncertainties in the exact timing of short-term events such as MVO and AVC may still remain. It might be possible that this uncertainty in timing may have contributed to our finding of relatively short isovolumetric relaxation time as seen in Fig. 4 [60 ms compared with the reported normal range by echocardiography, which is 76 ± 11 ms (13)]. Whereas a higher temporal resolution can be achieved by echocardiography, 3-D myocardial displacement cannot be measured using echo-Doppler. Midwall layers in the basal, midventricular, and apical levels were studied in our study. Despite the existence of regional heterogeneity in the magnitude of contraction and the timing of relaxation phenomenon, the differences were too small for detection by our MRI methods (3).

Systolic strain development is crucial to a complete understanding of events occurring during early diastolic relaxation given the intertwined sequence of myocardial deformation as cross-bridges release at end systole. Indeed, the temporal boundary between systole and diastole is artificial and difficult to define such that previous studies have classified myocardial events in the early relaxation period as part of the systolic phase (5, 23, 28). Hence, ventricular unfolding is best understood as part of a continuum with end-systolic myocardial deformation.

In conclusion, LV motion associated with myocardial relaxation is characterized by the release of mechanical energy stored during systole in the form of shear and torsion. This ventricular unfolding mechanism leads to radial thinning that occurs before aortic valve closure and the development of longitudinal and circumferential strains and ventricular filling. Thus shear and torsion forces and radial thinning produce the rapid reduction of LV pressure that induces early diastolic filling. Further understanding of diastolic strains and their intrinsic mechanisms during pathological conditions could enhance our ability to better conceptualize diastolic dysfunction.

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DISCLOSURES
This work was presented at the 75th meeting of the American Heart Association, November 2002, Chicago, IL.

REFERENCES


