Regional timing of myocardial shortening is related to prestretch from atrial contraction: assessment by high temporal resolution MRI tagging in humans

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Zwanenburg, J. J. M., M. J. W. Gütte, J. P. A. Kuijer, M. B. M. Hofman, P. Knaapen, R. M. Heethaar, A. C. van Rossum, and J. T. Marcus. Regional timing of myocardial shortening is related to prestretch from atrial contraction: assessment by high temporal resolution MRI tagging in humans. Am J Physiol Heart Circ Physiol 288: H787–H794, 2005. First published October 14, 2004; doi:10.1152/ajpheart.00610.2004.—Earlier studies have shown substantial nonuniformity in normal left ventricular (LV) myocardial function concerning both the degree of shortening and timing of shortening. We hypothesized that nonuniform LV function may be related to nonuniform prestretch induced by atrial contraction. Eleven healthy human subjects were studied using MRI myocardial tagging and strain analysis. The amount of circumferential prestretch was assessed in 30 LV segments. Prestretch was defined as the difference in strain between end diastole (at ECG R wave) and diastasis. Furthermore, both the degree of shortening (quantified as peak circumferential shortening, peak systolic shortening rate, and amount of postsystolic shortening) and timing of shortening (quantified as the onset time of shortening and time to peak shortening) were assessed. LV prestretch was found to be nonuniform, with the highest values in the lateral wall. The amount of segmental prestretch correlated significantly with peak shortening (r = 0.79), peak shortening rate (r = 0.50), amount of postsystolic shortening (r = 0.67), onset time of shortening (r = −0.57), and time to peak shortening (r = 0.71) (P < 0.001 for each of these relations). These relations may be explained by regional differences in wall stress or by a regional Frank-Starling effect. The correlation between timing of shortening and prestretch demonstrates that mechanical timing is not determined by electrical phenomena alone. In conclusion, regional variation in LV function correlates with the nonuniform prestretch from atrial contraction.

heterogeneity; mechanical asynchrony; strain; atrial systole

Several studies have demonstrated that left ventricular (LV) function is nonuniform in healthy human subjects (1, 19, 27). Peak shortening is larger in the lateral wall than in the septum and increases from the base to apex (19). Besides variations in the degree of shortening, variations in the timing of shortening have been reported including early onset and late peak of shortening in the lateral wall (31). A substantial number of regions reach peak shortening after aortic valve closure, leading to regions with postsystolic shortening in the normal heart (27, 31). Understanding the origin of normal regional differences in LV myocardial function may give insight in pathological nonuniformities. The nonuniformity in the timing of shortening is of particular interest, because in patients with heart failure and asynchronous contraction, resynchronization therapy with LV or biventricular pacing is applied (3, 4, 14), whereas the response to resynchronization therapy is difficult to predict (20).

Observations of considerable asynchrony in patients with narrow QRS widths imply that electrical phenomena are not the only determinant of the timing of shortening but that mechanical factors may also play an important role in the timing of myocardial shortening (10, 30). In addition, the observation in normal subjects that the pattern in the time to onset of shortening (T onset) differs from the pattern of electrical activation suggests that the timing of shortening is not determined by electrical phenomena alone (31). However, direct evidence for a relation between mechanical factors and the timing of myocardial shortening in the in vivo heart is lacking. We hypothesize that heterogeneity in prestretch induced by the atrial contraction contributes to the heterogeneity in myocardial function and timing. Regional myocardial function is probably linked to LV prestretch by heterogeneity in wall stress [due to differences in architecture, geometry, and material properties (1, 2, 21)] or the dependence of the developed force on end-diastolic sarcomere length [a local manifestation of the Frank-Starling mechanism (13, 16, 24)]. In the same way, regional timing of myocardial shortening may be related to LV prestretch. T onset occurs when the generated force overcomes the load against which the myocardium has to contract. In myocardium with higher prestretch, either the load (wall stress) is lower or the generated force is higher (due to a local Frank-Starling effect). Therefore, myocardium with higher prestretch is expected to show an earlier T onset.

In this study, MRI with myocardial tagging was used to assess the circumferential strain (εc) of the LV with high temporal resolution and to determine the spatial distribution of LV prestretch induced by the atrial contraction. We explored whether the prestretch shows regional variations and whether these variations are related to the regional degree of shortening and to the regional timing of shortening.

METHODS

Subjects

Eleven healthy subjects (mean age 41 ± 12 yr; 7 men and 4 women) with no history of cardiac disease, normal ECG, ejection fraction > 50%, and blood pressures under 160/90 mmHg were studied after informed consent was obtained according to our institutional guidelines.

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Imaging

The imaging protocol has been previously described in Ref. 31. In brief, myocardial tagging images with high temporal resolution (14 ms) were obtained by steady-state free precession imaging using the linearly increasing startup angle approach (32) to avoid artifacts. Complementary tagging (CSPAMM) was used for improved tag contrast and strain analysis (8, 17). Five short-axis image planes were acquired from base to apex, with 4 image series per plane: horizontally and vertically tagged images with both positive and negative sinusoidal tagging for CSPAMM. Breath hold misregistration was minimized using a multiple brief expiration breath hold scheme (5, 18). The four series of a single image plane were acquired in 4.5 min. The tag spacing was 7 mm. Examples of the complementary tagged images are shown in Fig. 1.

A long-axis cine in the three-chamber view was acquired to determine the closure time of the aortic valves (tavc). This cine had a temporal resolution of 14 ms and required a single breath hold, using steady-state free precession imaging with view sharing. Conventional nontagged short-axis cine images were acquired for measuring the LV volumes and ejection fraction. The acquisition duration of the complete protocol was ∼45–55 min/subject.

Postprocessing

Strain analysis. Strain analysis was performed using the harmonic phase method, as described previously (31). εc was calculated from the Lagrangian strain tensor as the percent change in length of a small line segment in the circumferential direction (9):

\[ \varepsilon_c = \left( \sqrt{1 + 2E_{cc}} - 1 \right) \times 100\% \]  

where \( E_{cc} \) is the Lagrangian strain component in the circumferential direction. The circumferential strain data were averaged in six circumferential segments: inferoseptal, anteroseptal, anterior, anterolateral, inferolateral, and inferior. Because the fibers at the midwall are mainly oriented in the circumferential direction and lay in the image plane (11, 28), only strain data from the mid-50% of the myocardial

![Fig. 1. Example images with myocardial complementary tagging (CSPAMM) obtained at a midventricular level in the short-axis orientation in a healthy subject. Anatomic images are shown at the top for clarity. Horizontally and vertically tagged images are shown 39 ms after the application of the tagging pattern (left), at end systole (middle), and during diastasis (right).](http://ajpheart.physiology.org/)

![Fig. 2. Example of circumferential strain (\( \varepsilon_c \); top) and the strain rate (\( d\varepsilon_c/dt \); bottom) obtained with MRI myocardial tagging. Because the undeformed tagging pattern is applied at time \( t = 0 \) (ECG R wave), the strain starts at zero level at \( t = 0 \). The physiological reference state, however, is assumed to be during diastasis, just after the rapid filling and before the onset of atrial systole (∼200 ms before next ECG R wave). Thus prestretch induced by the atrial contraction is defined as the difference between zero and the average strain plateau at diastasis (circled data points). The R-R interval of this subject was ∼1,050 ms.](http://ajpheart.physiology.org/)
The circumferential strain rate \( \frac{d\varepsilon_c}{dt} \) was calculated numerically from a copy of the \( \varepsilon_c \) curve that was filtered with a moving average filter of five sample width to reduce noise sensitivity. The filtered strain curve was used only for the calculation of the strain rates, not for the quantification of the amount or timing of shortening.

**Prestretch.** Because of prospectively gated triggering, no strain was measured during the last 150–200 ms of the R-R interval, in which the atrial contraction occurs. Prestretch was therefore measured as the difference in LV strain before and after atrial contraction. The prestretch was defined as the strain at the R wave minus the average plateau strain observed during diastasis, as illustrated in Fig. 2. For consistent assessment of the prestretch, the following algorithm was used. The onset of diastasis was defined regionally by the end of rapid relaxation and was determined as the zero crossing in \( \frac{d\varepsilon_c}{dt} \) after the peak positive \( \frac{d\varepsilon_c}{dt} \) (peak lengthening rate) in early diastole. To prevent inclusion of data points during atrial contraction, the end of diastasis was defined as 200 ms before the next ECG R wave, which was normally just outside the interval covered by the strain curve. If the strain curve did not cover the full diastasis, only the part covered was used, with a minimum duration of three strain samples. If the period of diastasis could not be determined for a certain segment,

### Table 1. Global function parameters of the healthy subjects

<table>
<thead>
<tr>
<th>Global Function Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-diastolic volume, ml</td>
<td>163±13</td>
</tr>
<tr>
<td>End-systolic volume, ml</td>
<td>76±19</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>96±17</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>58±4</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>125±3</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>78±5</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>60±7</td>
</tr>
</tbody>
</table>

Values are means ± SD.

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Fig. 3. Example of left ventricular (LV) \( \varepsilon_c \) curves of a healthy subject for 5 slices and 6 circumferential segments. The horizontal arrow on the strain axis indicates the strain during diastasis (physiological resting state after rapid filling and before atrial contraction). This horizontal arrow is omitted when the strain value at diastasis could not be determined by the automated routine. The strain difference between diastasis and the ECG R wave (at \( t = 0 \)) is a measure for the LV prestretch induced by atrial contraction. Note the larger amount of LV prestretch in the lateral wall compared with the septum. The R-R interval was 950 ms for this subject. The vertical arrow on the time axis indicates the time of aortic valve closure (\( T_{avc} \)). IS, inferoseptal; AS, anteroseptal; AN, anterior; AL, anterolateral; IL, inferolateral; IN, inferior.
because of either a persistent positive strain rate or insufficient coverage of the cardiac cycle, the amount of prestretch for that segment was regarded as missing.

Degree of shortening. To examine the regional myocardial function in relation to the prestretch, both the degree of shortening and timing of shortening were assessed for each of the six segments in each slice. The degree of shortening was quantified by the peak circumferential shortening, the peak systolic circumferential shortening rate (PCSR), and the amount of postsystolic shortening. Postsystolic shortening was defined as the occurrence of the peak shortening after aortic valve closure (31). The amount of postsystolic shortening was zero if peak shortening was reached before aortic valve closure and was \( \varepsilon_c(T_{\text{avc}}) - \varepsilon_c(T_{\text{peak}}) \) otherwise, where \( T_{\text{peak}} \) is the time of peak circumferential shortening.

Timing of shortening. The timing of shortening was quantified by \( T_{\text{onset}} \) and \( T_{\text{peak}} \). \( T_{\text{onset}} \) was defined as the beginning of the down slope of the \( \varepsilon_c \) curve and was determined by an automated fitting algorithm as described in detail previously (31). \( T_{\text{onset}} \) is reported in milliseconds from the ECG R wave, and \( T_{\text{peak}} \) is reported in ms from \( T_{\text{avc}} \).

Investigated Relations

The prestretch data of the subjects were averaged per segment to construct a mean prestretch map for the normal heart. Missing values were omitted in the calculation of the average prestretch per segment. Similarly, maps of peak circumferential shortening, PCSR, amount of postsystolic shortening, \( T_{\text{onset}} \), and \( T_{\text{peak}} \) were obtained. Linear regression analysis on the averaged data was used to investigate the relation between the LV prestretch and parameters of regional myocardial function. To obtain insight in the individual variability in the observed relations, individual correlation coefficients were calculated between the prestretch and each of the investigated parameters of myocardial function.

In addition, the factors by which prestretch influences peak shortening were explored. In vitro studies have shown that an increase in prestretch increases 1) the duration of shortening and 2) the shortening velocity at a constant afterload (22, 26), which both may enhance peak shortening. Therefore, multiple regression analysis was used with the peak shortening as a dependent variable and \( T_{\text{peak}} \), PCSR, and the product of \( T_{\text{peak}} \times \text{PCSR} \) as predictors. \( T_{\text{peak}} \times \text{PCSR} \) accounts for the interaction between \( T_{\text{peak}} \) and PCSR. The stepwise selection method was used to include or exclude a predictor from the model, using a probability < 0.05 as criterion to include a predictor and a probability > 0.1 as a criterion to exclude a predictor.

Statistics

Paired Student’s \( t \)-tests were applied to compare the prestretch between opposite myocardial segments (using the mean value of the 5 slices) and to compare between the apex and base (using the mean value of the 6 circumferential segments). The regression analysis described above was performed using SPSS software (SPSS for Windows, Release 11.5.0, SPSS; Chicago, IL). Values are presented as means ± SE for regression coefficients and as means ± SD otherwise. \( P \) values of <0.05 were regarded as significant.

RESULTS

Subjects

All subjects had a normal QRS width of 83 ± 15 ms (range: 63–114 ms). Table 1 shows the global function parameters of the subjects. For all subjects included in this study, prestretch could be determined in at least 24 of 30 segments (average number of missing segments per subject: 2.3 ± 2.0).

LV Prestretch: Amount and Distribution

An example of the \( \varepsilon_c \) curves for all segments for a single subject is shown in Fig. 3. Note the regional differences in the plateau strain at diastasis and consequently in the amount of prestretch induced by the atrial contraction. The map of the average LV prestretch is shown in Fig. 4. Table 2 summarizes the prestretch for the six circumferential segments averaged

Table 2. LV prestretch caused by atrial contraction

<table>
<thead>
<tr>
<th></th>
<th>IS</th>
<th>AS</th>
<th>AN</th>
<th>AL</th>
<th>IL</th>
<th>IN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prestretch</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prestretch, %</td>
<td>2.7±1.3</td>
<td>2.7±1.2</td>
<td>3.6±1.5</td>
<td>3.7±2.0*</td>
<td>5.5±1.7†</td>
<td>2.9±1.6‡</td>
</tr>
</tbody>
</table>

Values are means ± SD. LV, left ventricle; IS, inferoseptal; AS, anteroseptal; AN, anterior; AL, anterolateral; IL, inferolateral; IN, inferiorior. *\( P = 0.11 \), IS vs. AL; †\( P < 0.0005 \), AS vs. IL; ‡\( P = 0.13 \), AN vs. IN; §\( P = 0.13 \), apex vs. base.
over all five slices and shows in the clockwise direction a gradual increase in prestretch from the inferoseptal to the inferolateral segment. The difference between the apex and base was not significant. The highest prestretch was observed in the inferolateral segments (from apex to base) and the anterolateral and anterior segments at the apex. In each individual subject, the inferolateral prestretch was consistently larger than the anteroseptal prestretch.

Relation Regional Prestretch and Degree of Shortening

The spatial distribution of peak circumferential shortening was very similar to the distribution of prestretch, as demonstrated in Fig. 4. Linear regression revealed a close correlation between the amount of prestretch of a segment and the peak εc of that segment (r = 0.79, P < 0.0005; Fig. 5A). The correlation between the amount of prestretch and peak shortening rate was much weaker but still significant (r = 0.50, P = 0.005; Fig. 5B). Also, the amount of postsystolic shortening was correlated to the prestretch (r = 0.67, P < 0.0005; Fig. 5C). The regression parameters for the relations between prestretch and the parameters of the regional myocardial function can be found in Table 3.

The relations observed in the averaged data tended to be present also on an individual basis, although the correlation was not always significant. No significant correlations opposite to the relation of the averaged data were observed. The individual correlations between the LV prestretch and degree of shortening are shown in Fig. 6.

In the multiple regression analysis, Tpeak and PCSR were both excluded as independent predictors for peak shortening. Consequently, the combined predictor Tpeak × PCSR appeared as the best predictor for peak shortening, with a regression coefficient of 0.31 ± 0.06 (R² = 0.48, P < 0.0005).

Relation Regional Prestretch and Timing of Shortening

Tonset showed a weak but significant negative correlation with the amount of prestretch (r = −0.57, P = 0.001; Fig. 7A). This means that regions with more prestretch have an earlier onset of shortening. The duration of shortening was longer in regions with more prestretch, as can be seen from the positive correlation between Tpeak and prestretch (r = 0.71, P < 0.0005; Fig. 7B). The actual distributions of Tonset and Tpeak have been published previously (31). The relations between LV prestretch and timing of shortening were also observed on an individual basis, as can be seen from Fig. 6. For all subjects except one, at least two of five investigated relations were significant. None of the correlations that were opposite to the relations found for the average data were significant.

DISCUSSION

This study demonstrated in healthy human subjects that LV prestretch induced by the atrial contraction is not uniform. This nonuniformity in prestretch corresponds with the nonuniformity in both regional myocardial function and timing of shortening. The correlation between LV prestretch and timing of shortening is evidence for the hypothesis that mechanical factors also influence the timing of shortening, particularly because the pattern in the onset of shortening differs from the electrical activation pattern (6, 31).

LV Prestretch

The amount of prestretch ranged from 2.7 ± 1.3% in the septum to 5.5 ± 1.7% in the inferolateral segment. Ennis et al. (7) have reported strain measurements over the full cardiac cycle including the atrial contraction using a dedicated acquisition and reconstruction method. Although quantified in a

Table 3. Regression coefficients between parameters of regional LV myocardial function and regional prestretch

<table>
<thead>
<tr>
<th>Regional Function Parameter</th>
<th>Constant</th>
<th>Regression Coefficient</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak circumferential shortening</td>
<td>14.7±0.8%*</td>
<td>1.4±0.2*</td>
<td>0.62</td>
</tr>
<tr>
<td>Peak circumferential shortening rate</td>
<td>85.4±3.6%/s*</td>
<td>2.9±1.0 s⁻¹‡</td>
<td>0.25</td>
</tr>
<tr>
<td>Amount of postsystolic shortening</td>
<td>−1.4±0.8%§</td>
<td>1.0±0.2*</td>
<td>0.45</td>
</tr>
<tr>
<td>Time to onset of shortening</td>
<td>80.5±4.0 ms from ECG R wave*</td>
<td>−3.9±1.1 ms/§†</td>
<td>0.32</td>
</tr>
<tr>
<td>Time to peak shortening</td>
<td>−39.6±13.4 ms from Tavc*</td>
<td>19.0±3.6 ms/§*</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Values are means ± SE. Tavc, moment of aortic valve closure. *P < 0.0005; †P = 0.001; ‡P = 0.005; §P = 0.07.
different way, they found a similar pattern in the prestretch induced by atrial contraction, with lowest prestretch in the septum (2.8 ± 1.1%, n = 6) and highest prestretch in the lateral and inferior regions (3.8 ± 0.4% and 4.2 ± 1.0%, respectively). These highest values seem to be somewhat lower than found in this study, possibly because Ennis et al. used four instead of six circumferential segments, whereas the spatial variation in prestretch is relatively large in the lateral wall (Fig. 4 and Table 2).

Relation Regional Prestretch and Degree of Shortening

The spatial pattern in peak εc (Fig. 4B), with the largest peak shortening occurring in the lateral wall, is comparable to the pattern reported in literature (1, 19). A close correlation was observed between peak shortening and prestretch. The multiple regression analysis between the peak shortening and both Tpeak and peak shortening rate supports the idea that the prestretch influences peak shortening via two pathways. Prestretch increases peak shortening not only by prolongation of the duration of shortening but also by increasing the rate of shortening.

Besides the peak shortening and peak shortening rate, the amount of postsystolic shortening (the amount of shortening developed after aortic valve closure) is also influenced by prestretch. The regression coefficient of the relation between postsystolic shortening and prestretch (1.0 ± 0.2) is comparable to that of the relation between peak shortening and prestretch (1.4 ± 0.2; Table 3). This implies for the regions with most prestretch that the extra peak shortening due to the extra prestretch is only slightly larger than the simultaneous increase in postsystolic shortening and consequently only partially benefits ejection.

Relation Regional Prestretch and Timing of Shortening

The negative correlation between the regional T onset and LV prestretch implies that the force generated by the myocardial muscle overcomes the existing load earlier in a region with more prestretch than in a region with less prestretch. This is compatible both with local differences in wall stress and with a local manifestation of the Frank-Starling mechanism (length-dependent activation), as outlined in Fig. 8. In terms of local differences in wall stress (Fig. 8A), a lower wall stress will lead to more prestretch during diastole (as it makes the wall more compliant to the atrial contraction) and to a lower load against which the muscle has to contract during systole, which yields an earlier onset of shortening. In terms of a local Frank-Starling effect (Fig. 8B), an increase in initial segment length leads to a stronger contraction while peak force is reached at the same time (26), so that a given load is overcome earlier. Besides, prestretched regions can begin to shorten earlier by elastic recoil (25). The fact that the correlation between T onset and prestretch was rather weak (r = −0.57) may be due to regional differences in electrical activation and to noise in the T onset values.

The relation between Tpeak and LV prestretch can be explained in the same way as that for T onset. Both regional differences in wall stress and the Frank-Starling mechanism may be involved. It is interesting to consider the compatibility of the observations with a local Frank-Starling effect. The relation between Tpeak and prestretch is quite strong: Tpeak is increased by 19 ms/% prestretch (Table 3). If we assume that the sarcomere length during diastasis is 1.9 μm [slack length (23)], then the observed increase in Tpeak of 19 ms/% prestretch is equivalent to 1,000 ms/μm increase in sarcomere length (95% confidence interval from the SE in Table 3: 614–1,384 ms/μm sarcomere length). This value is comparable with the slope between twitch force duration and initial sarcomere length reported for rat cardiac trabeculae (24, 26). Twitch force duration increases by about 400 ms/μm increase in initial sarcomere length for isometric contraction (derived from Fig. 4 in Ref. 24 and Fig. 1 in Ref. 12) and by about 670 ms/μm increase in sarcomere length for isosmometric contraction (derived from Fig. 7 in Ref. 26). These literature values seem to be lower than the value found for Tpeak in this study (1,000 ms/μm). However, one should keep in mind that the data of the
force duration are obtained from right ventricular rat trabeculae at 25°C, whereas our data of $T_{peak}$ are obtained from the human LV in vivo, ignoring regional differences in electrical activation time. Furthermore, twitch force duration may only be directly comparable with $T_{peak}$ if the afterload is constant during shortening, which is clearly not the case as quite a few segments reach peak shortening after aortic valve closure (27, 31).

Clinical Implications

It has been shown that a simple wall stress model that incorporates only the geometry is insufficient to explain the regional variations in myocardial function in patients with nonischemic dilated cardiomyopathy (29). The close correlation between LV prestretch and peak shortening found in this study suggests that regional differences in material properties, myofiber structure, and contractile force should also be considered for a correct understanding of regional variations in myocardial function.

Previous work has shown that the onset of shortening has a pattern that is reversed to the pattern of electrical activation, with the earliest onset of shortening in the lateral wall (31). Our results show that the timing of shortening is related to the amount of LV prestretch due to atrial contraction and suggest that the influence of prestretch even dominates the influence of the electrical activation pattern in heart. Consequently, it may be very difficult to predict the response to resynchronization therapy and the optimal pacing position in patients with heart failure and conduction abnormalities, without extensive modeling by means of computer simulations (15, 25).

Limitations

It was assumed that the two-dimensional $e_c$ at midwall reflects myofiber behavior. For most slices this may be a good approximation, but especially toward the apex the midwall layer with circumferentially orientated fibers becomes thin, and an increasing amount of fibers will have a substantial longitudinal component (11). Because only the in-plane component of these fibers was observed in this study, the measured circumferential prestretch and shortening in the most apical slice may be less than the actual fiber stretch and shortening. Nevertheless, the relation between stretch and shortening is not affected as long as the angle of the fibers and the image plane is constant during the cardiac cycle.

Furthermore, we did not directly measure the strain during atrial systole but used the existence of the strain plateau during diastasis instead. The good agreement of our prestretch data with data obtained by Óênis et al. (7), who did measure strain evolution during atrial systole, justifies this approach.

In conclusion, atrial contraction leads to a nonuniform pattern of prestretch in the LV, with the most prestretch in the lateral wall. This prestretch is closely correlated to the nonuniformity present in both the amount and the timing of shortening. The effect of prestretch on the timing of shortening shows that synchrony of contraction is not determined by electrical synchrony alone but that mechanical aspects also play an important role.

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GRANTS

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