Magnetic Resonance Tissue Phase Mapping of Myocardial Motion
New Insight in Age and Gender

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Background—An exact understanding of normal age- and gender-matched regional myocardial performance is an essential perquisite for the diagnosis of heart disease. Magnetic resonance phase-contrast imaging (tissue phase mapping) enabling the analysis of segmental, 3-directional myocardial velocities with high temporal resolution (13.8 ms) was used to assess left ventricular motion.

Methods and Results—Radial, long-axis, and rotational myocardial velocities were acquired in 58 healthy volunteers (3 age groups, 29 women) in left ventricular basal, midventricular, and apical short-axis locations. For increased age, reduced ($P<0.003$) and prolonged long-axis and radial velocities ($P<0.05$) during diastole and reduced long-axis velocities ($P<0.001$) and apical rotation ($P<0.005$) during systole were found for both genders. Women demonstrated a reduced systolic twist ($P=0.009$), apical rotation ($P=0.01$), and systolic radial velocities ($P<0.02$) compared with men. Segmental analysis of long-axis motion with aging revealed differences in regional reduction of systolic (lateral 52% versus 30%) and diastolic (lateral 57% versus 41%) velocities in women compared with men. In basal segments, young women demonstrated higher long-axis velocities (+11% during diastole) than men, whereas this difference was reversed in older subjects (same segments, −20%). In addition, increased age resulted in a prolonged time to peak diastolic apical rotation ($P<0.04$) in women compared with men.

Conclusions—Age and gender strongly influence regional myocardial motion. Tissue phase mapping provides a comprehensive quantitative analysis of all myocardial velocities with high temporal and spatial resolution. The knowledge of the detected age- and gender-related differences in myocardial motion is fundamental for further investigations of cardiac disease.

Clinical Trial Registration—http://www.zks.uni-freiburg.de/uklreg/php/suchergebnis_all.php. Identifier: UKF001739 (Circ Cardiovasc Imaging. 2010;3:54-64.)

Key Words: magnetic resonance imaging ■ myocardial contraction ■ aging ■ gender

Volumetric analysis of the left ventricle based on MRI has been established as a reference standard for the determination of left ventricular (LV) performance. However, early changes in LV motion and regional pathologies may be overlooked by these global parameters because they do not reflect diastolic function or segmental contractility, which are not uniform within the healthy LV. Therefore, a complete segmental analysis of velocities is preferable to detect subtle changes in LV motion. Quantitative noninvasive assessment of regional myocardial performance still remains challenging. Myocardial velocities and derived parameters mainly based on tissue Doppler imaging were suggested as markers for LV contractility and diastolic function. However, because tissue Doppler velocity analyses do not allow assessing all myocardial velocity components, ie, radial, long-axis, and rotational motion for the different LV regions, MRI applications have been developed as alternatives. Magnetic resonance tagging and phase-contrast imaging have been used to assess myocardial motion. A recently published MR tagging study reported age-related alterations of regional myocardial strains. Aging has an enormous effect on cardiac disease and influences myocardial structure, resulting in a reduced number of enlarged cardiomyocytes and increased collagen content. These structural changes and differences in Ca channel handling, degeneration of sympathetic nerves, and reduction of arterial compliance and endothelial function affect LV function with increased age. However, the extent of altered LV function is still debated, and to date, gender, another factor of influence, is neglected.

Clinical Perspective on p 64
In contrast to previous MRI applications that suffered from limited temporal resolution and time-consuming data postprocessing, advances in MR sequence design based on navigator-gated MR tissue phase mapping (TPM) now enable an improved robust quantitative analysis of myocardial velocities during systole and diastole with high temporal resolution. Because TPM relies on a pixel-wise velocity mapping, it permits a detailed assessment of regional LV velocities in all spatial directions and with high spatial resolution covering the entire left ventricle. In an initial study with the same study population, we could recently show that TPM enables a complete visualization of LV motion and that a correlation analysis of the data might be useful to detect local differences of myocardial velocities.

The aim of this study is to analyze myocardial motion on a segmental basis to define the influence of age and gender on LV performance in healthy volunteers. For clinical application, it is essential to develop an understanding of the distribution and dynamics of normal myocardial velocities.

Methods

Study Population

Sixty-two healthy volunteers (32 men and 30 women) without history, symptoms, or medication of cardiovascular or pulmonary disease, diabetes, arterial hypertension, or peripheral arterial disease were included in the study. Written informed consent was obtained from all volunteers, and the study was approved by our local ethics board. Three volunteers were excluded because TPM data could not be acquired for technical reasons or claustrophobia. One man had to be excluded because of increased LV wall thickness and elevated blood pressure (BP). All included volunteers (n = 58, 29 men and 29 women) had normal left and right ventricular dimensions, regular blood pressure (BP). All included volunteers (n = 58, 29 men and 29 women) had normal left and right ventricular dimensions, regular blood pressure (BP). All included volunteers (n = 58, 29 men and 29 women) had normal left and right ventricular dimensions, regular blood pressure (BP).

Data Acquisition

All measurements were performed using a 1.5-T MR system (Magnetom Sonata, Siemens Medical Solutions, Germany) using a black blood k-space segmented gradient echo sequence (repetition time, 6.9 ms; flip angle, 15°; bandwidth, 650 Hz/pixel). Spatial resolution was 1.3 × 1.3 mm (96 × 256 matrix interpolated to 192 × 256). All data were acquired in basal, midventricular, and apical short-axis planes (slice thickness, 8 mm). Velocity encoding was performed with velocity sensitivity of 15 cm/s in-plane and 25 cm/s through-plane. Measurements were performed using prospective ECG gating and respiration control based on advanced navigator as previously described. Sequential acquisition of reference and motion-sensitized scans in combination with view sharing (ie, in consecutive cardiac cycles) resulted in a temporal resolution of 13.8 ms.

Data Analysis

Data analysis was performed using home-developed software package (programmed in Matlab, The Mathworks Inc, Natick, Mass). After manual segmentation of epicardial and endocardial contours, a correction for bulk motion was performed. In brief, a correction based on subtraction of global translation velocities from the local velocity components was applied. Global velocities were determined by individually averaging myocardial Cartesian velocity components in regions exhibiting low velocities along the same Cartesian direction. Next, the measured 3-directional myocardial velocities were transformed into an internal polar coordinate system positioned at the center of mass of the segmented left ventricle. As a result, radial velocities, rotational velocities, and long-axis velocities of the left ventricle could be assessed (Figure 1).

Figure 1. Schematic illustration of the analysis strategy for global and segmental myocardial velocities. An extended American Heart Association 16-segment model, including epicardial and endocardial regions was used for the presentation of the regional dynamics. For each short-axis location, global velocity time courses were calculated and analyzed as illustrated for basal long-axis velocities in men.

To analyze global cardiac motion, velocity components were averaged over the entire slice, resulting in velocity time courses in basal, midventricular, and apical locations for each volunteer (Figure 1). For each gender and age-group, the obtained time courses were averaged over all volunteers for each acquired slice and each velocity component. Further analysis included the calculation of peak systolic and peak diastolic velocities of long-axis motion and radial contraction. In addition, time-to-peak (TTP) systolic and diastolic durations were extracted from the velocity time courses. To analyze the global rotational LV motion, peak rotation as averaged over the apical slices and...
velocities were calculated (Figure 2).

For the segmental analysis, the anteroseptal right ventricular connection of the LV was marked manually. Next, the LV was divided according to the 17-segment model (Figure 1). We analyzed 6 basal, 6 midventricular, and 4 apical regions excluding the 17th apical segment. Each segment was subdivided into an endocardial and epicardial region (Figure 1). For each segment, peak and TTP radial and long-axis velocities in systole and diastole were calculated and averaged for each gender and age group. Results are presented as bulls eye plots permitting a direct comparison between genders, age, and short-axis location (Figures 3 through 5).

Statistics
All data are presented as mean ± SD unless stated otherwise. Because Q-Q plots demonstrated normal distribution, the differences between the 3 age groups were analyzed using a 1-way ANOVA followed by a Holm-Sidak test for pairwise multiple comparisons (plots not shown). The given probability values in the text and tables represent values unadjusted for multiple testing. Therefore, the results should be interpreted with caution because some of the findings may have occurred by chance as a result of multiple testing. Comparisons between genders were performed by t test. Correlations between velocities and the independent variables were calculated by the Pearson product moment correlation. To select variables for multiple linear regression analysis, the Akaike criterion (P ≤ 0.15.7%) was used. Statistical testing was performed using SigmaStat for Windows version 3.10. Two-tailed tests with P < 0.05 were considered statistically significant.

Results
Volunteer Data
The clinical characteristics of all volunteers are summarized in Table 1. LV ejection fraction and BP were higher, and LV end-systolic volumes were lower in group 3 compared with the younger age groups (P < 0.05). Gender-specific analysis of the age groups demonstrated increased LV volumes and lengths in younger women than in older female volunteers. LV lengths and LV end-diastolic diameters (LVEDD) differed significantly between genders in all age groups, whereas LV end-systolic volumes, LV end-diastolic volumes, and LV mass differed only between genders in group 2 and 3. In group 3, additional significant differences in heart rate, diastolic BP, and stroke volume were found between genders.

Systolic Motion
Long-Axis Velocities
Global peak systolic long-axis velocities were significantly reduced for age >40 years (P < 0.001; for cumulative results, see Table 2 and supplemental Table I). Results of the segmental analysis of long-axis velocities are shown in Figure 3 for peak velocities and in Figure 4 for TTP velocities. Systolic long-axis velocities were highest in basal (infero-) lateral segments and decrease toward the apex and anteroseptal regions in all age groups. No relevant intramural gradients between epicardial and endocardial velocities during systole or diastole were seen.

The intraventricular velocity gradients between lateral and septal basal regions were slightly reduced with increased age. Reductions in systolic long-axis velocities with increased age were most pronounced in anterior and lateral regions and more prominent in the female group (Figure 3). In lateral regions, velocities decreased by 52% (8.1 versus 3.9 cm/s) in women of age group 3 compared with the youngest age, whereas the decrease was only 30% (7.9 versus 5.5 cm/s) in men. Women in the oldest age group presented with reduced velocities in most segments (mean in basal anterior and lateral regions, -29%) compared with men. In contrast, systolic long-axis myocardial velocities of basal anterior and lateral segments in young women exceeded those in men (basal anterior and lateral mean, +8%). Furthermore, a more pronounced age-related systolic TTP prolongation was observed in women (Figure 4).

Radial Velocities
Gender-specific differences were detected for global systolic radial velocities, which were significantly decreased in women compared with men (P = 0.024). Segmental systolic radial velocities were lowest in the apex (results not shown). For all age groups, endocardial peak radial velocities exceeded the velocities of the epicardial segments. Systolic TTP also demonstrated higher values for basal and midventricular endocardial regions in nearly all segments.

Apical Rotation and Velocity Twist
The analysis of rotational LV velocities revealed complex motion patterns. The base of the left ventricle changed direction of rotation up to 6 times, whereas the apex performed a counterclockwise rotation during systole and a clockwise reversed rotation during diastole as viewed from the apex, resulting in multiple wringing motions of the heart (supplemental Figure). Counterclockwise (systolic) rotation
was more pronounced in the epicardial regions. The difference between basal and apical rotation velocities (velocity twist) is shown in Figure 2.

With increased age, the systolic early rapid untwist (open arrow) disappeared. Systolic twist was considerably lower in women (2.05 cm/s) compared with men (2.46 cm/s, $P/H0.009$). Systolic apical rotation demonstrated an age-related decrease and significant delay ($P<0.05$) regarding peak velocities during systole for both genders, whereas twist was only reduced in women with increased age ($P=0.02$, group 1 versus group 3).

### Diastolic Motion

**Long-Axis Velocities**

Segmental analysis revealed overall maximum velocities during diastole in basal and lateral regions in all age groups. Apical velocities reached $\approx 40\%$ of the basal velocities, and lateral segments exceeded septal velocities in all age groups. No relevant intramural gradients between epicardial and endocardial velocities during systole or diastole were seen.
Global diastolic long-axis velocities were markedly reduced \((P<0.003)\) in the older volunteers (Table 2 and supplemental Table 1). Regional diastolic velocities were reduced with increased age in all segments and for both genders to various extents, but most pronounced in midventricular segments and in women also in basal regions (Figure 3). However, similar to systolic longitudinal velocities, the age-related differences are more evident in women. The reduction of velocities in lateral segments was 57% in women and 41% in men. Interestingly, women revealed higher diastolic peak velocities than men in young age in all segments except the apex (14.2 cm/s versus 13.0 cm/s in basal anterior and lateral regions), whereas this difference was reversed in the oldest group (6.8 cm/s versus 8.5 cm/s in basal anterior and lateral segments). Age-related delay in diastolic TTP velocities was distributed inhomogeneously within the LV, increased in septal and most midventricular regions of both genders (Figure 4).

**Radial Velocities**
Global radial expansion was markedly reduced \((P<0.02)\) and delayed \((P<0.05)\) in the older volunteers (Table 2 and supplemental Table 1). Segmental diastolic radial peak velocities and corresponding TTP for each gender and age

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**Figure 4.** Comparison of TTP peak systolic (top) and diastolic (bottom) long-axis velocities for different genders (rows) and age groups (columns) as color-coded overlay onto an extended American Heart Association 16-segment model including epicardial and endocardial regions.
group are shown in Figure 5. Diastolic radial velocities exceeded systolic velocities in younger volunteers and were consistently lowest in the apex and the basal septum. Consistent with results from global velocity analysis, diastolic velocities were reduced in most segments and delayed (except the basal septal wall) with increased age (Figure 5) for both genders.

**Apical Rotation and Velocity Twist**
Clockwise (diastolic) rotation of the apex was more pronounced in subendocardial segments. The diastolic overshoot of twist observed in young males (solid black arrow, Figure 2) was much less prominent in young females and was prolonged with age. Diastolic TTP apical rotation was delayed in older volunteers ($P<0.02$), which was due to delayed velocities in women with increased age ($P<0.04$).

**Correlations With LV Geometry, Global Function, Heart Rate, Blood Pressure, or Age**
After adjustment for other variables of influence, age was the only predictor for changes in systolic ($P=0.008$,
Table 1. Clinical Characteristics for All Volunteers

<table>
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<td>Women (n=9)</td>
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<td>BSA, m²</td>
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<td>1.9±0.2</td>
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<td>Heart rate/min</td>
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<td>LV-EF, %</td>
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<td>96.4±5.1</td>
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Data are presented as mean±SD. BSA indicates body surface area; EF, ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume.

*P<0.05 versus men.
†P<0.05 versus age group 1.
‡P<0.05 versus age group 3.

 correlation coefficient (R) = −0.64 for basal, R = −0.73 for midventricular, and R = −0.68 for apical regions) and diastolic (P<0.001, R = −0.79 for basal, R = −0.81 for midventricular, and R = −0.68 for apical regions) long-axis peak velocities and in systolic apical rotation (P=0.02, R = −0.65). Furthermore, peak diastolic radial velocities demonstrated a strong correlation with age (P<0.03, R = −0.71 for basal and midventricular, R = −0.50 for apical regions) after multiple linear regression and TTP diastolic twist was significantly influenced by gender (P<0.001, R = 0.66). Peak radial velocities (P<0.02, R = 0.67 for basal, R = 0.63 for midventricular and R = 0.66 for apical regions) and TTP systolic apical rotation (P=0.03, R = −0.34) correlated with LVEDD. Furthermore, multiple linear regression analysis revealed that heart rate correlated with all TTP velocities (P<0.05) except TTP systolic long-axis motion and apical rotation.

The results of the Pearson product moment correlation analysis are demonstrated in supplemental Table IIa and IIb. BP influenced diastolic radial and long-axis peak, TTP diastolic long-axis and TTP systolic twist velocities (P<0.05). TTP diastolic radial and long-axis velocities, systolic twist, and TTP diastolic apical rotation correlated with age, systolic peak radial, and rotational velocities and TTP diastolic rotation weakly correlated with gender. Peak systolic long-axis (P<0.02) and radial velocities (P<0.05) as well as apical rotation (P=0.0002) correlated positively with LV stroke volumes, and peak systolic long-axis velocities were negatively correlated with LV ejection fraction (P<0.02). Peak diastolic long-axis velocities were also negatively correlated with LV ejection fraction (P<0.05) and positively correlated with stroke volume (P<0.05). These correlations did not reach significance after multiple regression analysis in our study group.

The most important findings of this study regarding age- and gender-related changes in systolic and diastolic myocardial motion are summarized in Figure 6.

**Discussion**

LV function is one of the most prognostic determinants of cardiac diseases, and an exact analysis of myocardial performance is crucial for patients with heart disease.
To date, mainly tissue Doppler was used to evaluate myocardial velocities. Echo tissue Doppler velocity analysis of myocardial motion, including strain and strain rate imaging, have proven to be useful tools during the past decades, but these methods are limited by the operator dependency and the acoustic window of the patient. A major drawback is thus related to the impossibility to assess all myocardial velocity components, ie, radial, longitudinal, and circumferential motion, and LV regions. The MRI method used in this study (TPM) was previously validated and low inter- and intraobserver variabilities were demonstrated. It combines the advantages of MRI over tissue Doppler based techniques, as the robust technique with coverage of the entire ventricle, high spatial resolution, the possibility to measure all velocity components and to correct for the bulk motion of the heart with the high temporal resolution of 13.8 ms, which enables a comprehensive quantitative analysis of myocardial function. To our knowledge, this is the first study to show a detailed evaluation of age- and gender-specific normal LV function based on a regional analysis of myocardial velocities covering the 16 segments of the left ventricle.

The results of our study demonstrated a previously not described more pronounced decline of systolic and diastolic long-axis motion in women compared with men. Furthermore, we provided a description of distinct age-related changes in myocardial velocities, including reduction and delay of diastolic radial and long-axis velocities, reduction of systolic long-axis velocities on a segmental basis, and decreased and delayed apical rotation (Figure 6).

Diastolic Velocities
Diastolic function is often the first parameter altered in the course of cardiac diseases, before systolic function is affected. The velocities derived from TPM data reflect various aspects of diastolic function. Magnitude and timing of radial velocities are closely correlated with early LV filling. Peak long-axis velocities and peak diastolic rotation preceed LV filling and are components of the isovolumic relaxation period. Both peak long-axis and rotational velocities correlate well with the active LV relaxation and its invasive gold standard, the early diastolic pressure decay Tau. These velocities might therefore promote early diastolic filling by producing an apico-basal pressure gradient. Altered long-axis velocities as well as delayed and decreased diastolic rotation have already been described as early signs of myocardial dysfunction in a variety of myocardial pathologies, highlighting the clinical value of a noninvasive imaging technique assessing these velocity components. Our data showed that diastolic velocities are altered significantly with increased age irrespective of gender. Peak radial as well as peak long-axis velocities were considerably reduced in most segments alongside with an increase in time to peak velocities in both genders. Regional aspects of these age-related differences have been described before. In this study, we provided a complete 16-segmental analysis demonstrating that the distribution of velocities within the LV was retained with aging. Such age-related changes in peak velocities persisted even if differences in LV geometry or BP were taken into account.

Our observation of increased diastolic long-axis velocities in young women in nearly all segments and of reduced velocities in women of age group compared with men corresponds well with previous reports describing improved diastolic function in young women and reduced diastolic function compared with men with increased age. Decreased diastolic compliance and a steeper age-related increase in systolic and diastolic vascular and ventricular stiffness in women have been suggested as possible causes of the higher prevalence of diastolic heart failure. In accordance with the literature, we did not find significant age- or gender-related changes in peak diastolic rotation or untwist, but we demonstrated an age-related delay in diastolic apical rotation in women. Conflicting reports of reduced untwist and diastolic rotation in previously performed MR tagging studies might be related to limited temporal resolutions of approximately 40 ms, which may have limited the detection of peak velocities and thus exact definition of timing and magnitude of diastolic untwist.
Systolic Velocities

Several studies suggested that systolic velocities are altered in cardiac diseases, even if global systolic function is preserved.34 For gender-related differences in systolic function conflicting data exist, with most studies reporting increased global functional parameters in women compared with men.35 However, normal global systolic function does not exclude depressed single parameters of contractility.34 Our data demonstrated that age and gender have a significant effect on systolic myocardial velocities. Women demonstrated reduced twist, apical rotation, and radial velocities compared with men. With increased age, long-axis shortening was reduced in most segments, and apical rotation was delayed and diminished, whereas systolic twist remained unchanged in men, but not in women.

Notably, irrespective of gender and after adjustment to LV geometry and LV mass, age was the main predicting factor in a multiple regression model for apical rotation and systolic long-axis velocities. Conflicting data have been reported regarding systolic function with respect to increasing age.11,36 Age-related reductions of long-axis velocities in posterolateral and septal regions have been described.25 However, we demonstrated a stronger decline in systolic long-axis velocities for women with increased age (e.g., −52% in lateral regions compared with −30% in men). With regard to long-axis velocities, an earlier tissue Doppler imaging (TDI) study did not find significant gender related differences.11 However, only 1 velocity component in 2 segments was studied, and no segmental analysis with complete LV coverage was performed. The LV function in women is dependent on the hormonal status,37 a fact that might explain contrasting reports with respect to systolic function in women and underlines our findings of higher velocity alterations with aging in women.

In contrast to previous studies,7,33 we demonstrated a decrease in apical rotation velocity with aging. Again, this might be explained by the lower temporal resolution used in these studies (35 to 45ms) because high temporal resolution is thus necessary to reliably detect the very early first peaks (see online-only Data Supplement). Systolic LV rotation or torsion was described as markers of LV contractility, correlating well with invasive measurements,38 but as we demonstrated, these parameters were reduced in women and were highly influenced by age.

Correlations to LV Dimensions, Heart Rate, and Blood Pressure

For all altered peak velocities, age was the main predicting factor in multiple regression analysis. In addition to age, long-axis velocities demonstrated correlations (without reaching significance in multiple linear regression analysis) with LV length, LVEDD, and BP. Differences in these parameters did not explain the increased decay of long-axis motion with higher velocities in young women compared with men because LVEDD and LV length were lower in women compared with men in all age groups, and LVEDD and BP were not significantly altered with increased age in separate gender analysis. Moreover, differences of heart rate did not account for the detected gender dependency of the timing of diastolic rotation.

Limitations

Although this is the first study evaluating all segmental myocardial velocity components in healthy volunteers subdivided in age and gender, no data on pathologically altered LV performance have been presented. Previous studies using earlier implementations of TPM have already demonstrated altered velocities in cardiac diseases17,21,39 The results from these studies in small numbers of patients indicate the potential of TPM to detect altered myocardial dynamics associated with disease. Nevertheless, more studies are needed to provide further evidence that the presented technique can be of value in the investigation of cardiac disease.

In this study, we did not normalize for heart rate but analyzed time to peak velocities in absolute times because one aim of the study was to define which velocity components correlate to heart rate. However, heart rates did not differ between age groups and thus do not explain the gender-related finding. Furthermore, even with the careful patient selection applied in this study, an interaction of unknown heart disease cannot be completely excluded.

Clinical Implications

Myocardial velocities reflect contractility and diastolic function, correlate with invasive measurements, and are of prognostic value.40 The knowledge of their distribution and timing within the healthy left ventricle is essential for the exact understanding of heart disease. The growing impact on the issue of LV synchronicity further stresses the necessity to apply MRI methods with high temporal resolution.

Conclusion

In conclusion, our method enables a comprehensive analysis of all myocardial velocities covering the entire LV with high temporal and spatial resolution. Our data clearly demonstrate that age and gender has an important effect on myocardial performance. The extensive differences in myocardial performance with aging and in relation to gender form an essential base for further patient studies and may help to further elucidate the complexity of the performance of the heart muscle.

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Disclosures

None.

References


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**CLINICAL PERSPECTIVE**

Myocardial velocities reflect contractility and diastolic function, correlate with invasive measurements, and are of prognostic value in patients with heart disease. The knowledge of their distribution and timing within the healthy left ventricle is essential for the exact understanding of heart disease. Echo-based methods are limited by the dependency on the Doppler angle and the acoustic window of the patient. The MRI method used in this study (tissue phase mapping) is a robust technique allowing the evaluation of all myocardial velocity components with full ventricular coverage and a high temporal resolution of 14 ms. We showed that aging has a significant effect on systolic and diastolic myocardial function, including all velocity components. Furthermore, gender plays an important role in left ventricular motion. The pronounced age and gender related differences we describe stress the necessity of age and gender-matched control groups in studies evaluating myocardial function.