Diastolic Dysfunction in Women With Signs and Symptoms of Ischemia in the Absence of Obstructive Coronary Artery Disease
A Hypothesis-Generating Study

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Background—Angina, in the absence of obstructive coronary artery disease, is more common in women, is associated with adverse cardiovascular morbidity and mortality, and is a major burden to the healthcare system. Although advancements have been made to understand the mechanistic underpinning of this disease, the functional consequence remains unclear.

Methods and Results—Cardiac magnetic resonance imaging was performed to assess left ventricular function in 20 women with signs and symptoms of ischemia, but no obstructive coronary artery disease (cases), and 15 age- and body mass index–matched reference controls. Functional imaging included standard cinematic imaging to assess left ventricular morphology and global function, along with tissue tagging to assess left ventricular tissue deformation. Systolic function was preserved in both cases and controls, with no differences in ejection fraction (mean±SE: 63.1±8% versus 65±2%), circumferential strain (−20.7±0.6% versus −21.9±0.5%), or systolic circumferential strain rate (−105.9±6.1% versus −109.0±3.8% per second). In contrast, we observed significant differences between cases and controls in diastolic function, as demonstrated by reductions in both diastolic circumferential strain rate (153.8±8.9% versus 191.4±8.9% per second; P<0.05) and peak rate of left ventricular untwisting (−99.4±8.0° versus −129.4±12.8° per second; P<0.05).

Conclusions—Diastolic function is impaired in women with signs and symptoms of ischemia in the absence of coronary artery disease, as assessed by cardiac magnetic resonance tissue tagging. These results are hypothesis-generating. Larger studies are needed to define the exact mechanism(s) responsible and to establish viable treatment strategies.

Key Words: diastole ■ magnetic resonance imaging ■ myocardial ischemia ■ women

Signs and symptoms of ischemia in the absence of obstructive coronary artery disease (CAD) represent an important clinical problem, especially for women. Indeed, women with signs and symptoms of ischemia, but without obstructive CAD, are at increased risk for adverse cardiovascular events compared with asymptomatic community-based women.1 Moreover, symptom-driven health care is costly, with average lifetime cost estimates of $750,000.2


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The Women’s Ischemia Syndrome Evaluation (WISE), designed to investigate new and innovative techniques for the detection of ischemic heart disease in women,3 described an abnormal metabolic response to mild stress testing using 31P magnetic resonance (MR) spectroscopy in women with signs and symptoms of ischemia but no obstructive CAD.4 We and others have subsequently found this abnormality to be related to abnormal coronary reactivity,5,6 microvascular coronary dysfunction,7,8 and plaque erosion/distal microembolization.9,10 Despite this background, it remains unclear whether these abnormalities manifest into actual changes in ventricular function.

Accordingly, we incorporated MR tissue tagging into our standard MR imaging protocol to assess left ventricular (LV) systolic and diastolic function. MR tissue tagging is an accurate noninvasive imaging technique that provides detailed quantitative information about myocardial tissue deformation.11,12 The application of this technique to a variety of different diseases has allowed for the early detection of subclinical LV dysfunction13,14 and, more recently, for the assessment of diastolic function.15,16 We hypothesized that women with angina in the absence of obstructive CAD would have...
impaired diastolic function, but preserved systolic function, compared with a group of age-matched reference controls.

Methods

Study Population
The population consisted of 20 women (median age, 60 years) who were evaluated at Cedars-Sinai Medical Center for signs and symptoms of ischemia and had no obstructive CAD (defined as coronary stenosis of >20% in any epicardial coronary artery). Women were enrolled in the National Heart, Lung, and Blood Institute–sponsored WISE-Cardiovascular Dysfunction Study, and their coronary angiograms were reviewed by the angiographic core laboratory. These women underwent cardiac MR imaging (MRI) for LV function and perfusion imaging.

Exclusion criteria included acute myocardial infarction (<30 days), planned percutaneous intervention or coronary bypass surgery, primary valvular disease, cardiogenic shock or intra-aortic balloon pump, New York Heart Association class III or IV heart failure, ejection fraction <40%, hypertrophic cardiomyopathy, severe renal or liver disease, pregnancy, life expectancy <6 months, and contraindications to angiography (hypersensitivity to contrast, active bleeding, bleeding diathesis, renal dysfunction). A reference control group of 15 women (median age, 56 years) was also recruited to serve as control subjects for the MRI. The reference control group had no cardiac risk factors according to the National Cholesterol Education Program guidelines, had no evidence of heart disease on the basis of a normal maximal exercise treadmill stress testing (Bruce protocol), and did not possess any of the clinical conditions described in the exclusion criteria above. All subjects provided informed consent, and their physicians approved their participation.

MRI
Cardiac MRI was performed in the supine position on a 1.5-T MR scanner (Avanto; Siemens Healthcare, Erlangen, Germany) with ECG gating and a phased-array surface coil (CP Body Array Flex; Siemens Healthcare). A highly standardized protocol was used and included assessment of LV morphology and function, in addition to pharmacological stress and rest first-pass myocardial perfusion imaging with a total gadolinium-based contrast dose of 0.1 mmol/kg (Optimark; Mallinckrodt, St Louis, MO). Blood pressure and pulse oxygenation were monitored (Invivo, Philadelphia, PA) and recorded before, during, and after adenosine infusion. A 12-lead ECG was recorded before and after MRI. Subjects had caffeine withdrawn for 24 hours before the examination.

LV Function
Breath-hold cine MRI using balanced steady-state free precession was acquired covering the left ventricle with a stack of 10 to 12 short-axis slices from base to apex, as well as one 4-chamber long-axis and one 2-chamber long-axis image (field of view, 350 mm; temporal resolution, 44.4 ms; echo spacing, 3.2 ms; echo time, 1.3 ms; flip angle, 80°; slice thickness, 8.0 mm; 2 mm gap; 25 cardiac phases; 2-fold TGRAPPA parallel imaging). Tagged short-axis images were also acquired using a gradient echo sequence (breath-hold scan; field of view, 400 mm; temporal resolution, 19.6 ms; echo spacing, 4.0 ms; echo time, 2.78 ms; flip angle, 14°; slice thickness, 8.0 mm; 2-fold TGRAPPA parallel imaging). Two sets of scans for 4 adjacent short-axis slices were acquired, covering the entire left ventricle from base to apex. The first set of grid tags focused on systolic function by triggering the tagging sequence at end-diastole (R wave of ECG). Tissue tags fade after ~400 to 500 ms due to T1 relaxation, which could adversely affect the interpretation of diastolic indices that normally occur at this time. To overcome this potential limitation, we acquired a second set of grid tags with a trigger delay set to end-systole (defined as the smallest ventricular cavity area), thus ensuring optional tag quality throughout diastole.

LV Perfusion and Delayed Enhancement Imaging
As previously described, the LV short axis was determined by scout imaging, and first-pass perfusion images were obtained in basal, mid, and distal short-axis image planes. A gradient echo-echo planar imaging hybrid pulse sequence was used for all patients (field of view, 350 × 350 mm2 or minimized dependent on patient size; slice thickness, 8 mm; TR/TE maximum, 6.5/1.3 ms; receiver bandwidth, 1420 Hz/pixel; 2-fold TGRAPPA parallel imaging; temporal resolution, 1 heartbeat). For pharmacological stress, adenosine (Adenoscan; Astellas Pharma US, Inc, Northbrook, IL) was injected at a dose of 140 μg/kg per minute intravenously over a total duration of 4 minutes. Then 0.05 mmol/kg of Gd-DTPA was administered (2 minutes later) via a second intravenous catheter at a rate of 4 mL/s, followed by 30 mL saline flush at the same rate. After a 10-minute wait to allow for contrast washout, rest perfusion imaging was performed with the same contrast settings. Delayed contrast enhancement images—10 to 12 short-axis slices, 1 horizontal long-axis slice, and 1 vertical long-axis slice at the same positions as the LV function cine images—were obtained 10 minutes after to identify regional fibrosis.

MRI Analysis
Using commercially available software (CAAS MRV 3.3; Pie Medical Imaging B.V., Maastricht, the Netherlands), LV mass, LV volume, and LV early peak filling rate and time to peak filling rate were assessed by manually tracing the epicardial and endocardial borders of the short-axis cine images as previously described. Stroke volume was calculated as end-diastolic volume minus end-systolic volume. Ejection fraction was calculated as stroke volume divided by end-diastolic volume. LV mass was indexed to end-diastolic volume to evaluate LV concentricity.

As illustrated in conceptual Figure 1, tissue tagging analysis was performed by manually tracing the epicardial and endocardial borders of each slice, using commercially available software (HARP; Diagnosoft). Circumferential strain and its time derivative in systole and diastole were calculated, along with the peak rate of rotation across the 2 most distal LV slices (base and apex) in diastole (referred to as the peak untwisting rate). Our in-laboratory intrarater reliability for measuring peak circumferential strain, systolic circumferential strain rate, diastolic circumferential strain rate, and peak untwisting rate, reported as a coefficient of variation, was 2.1%, 3.6%, 4.2%, and 4.3%, respectively.

Quantitative analysis of the first-pass perfusion images for the assessment of myocardial perfusion reserve index (MPRI) was performed by an experienced investigator using CAAS MRV 3.3 software (Pie Medical Imaging B.V.). Epicardial and endocardial LV myocardial contours (basal, midventricular, and apical slices) were manually traced to acquire intensity over time curves at rest and stress for 16 segments (segment 17, the LV apex, was not imaged). The calculated relative upslope (maximum upslope of the myocardial signal enhancement divided by the maximum upslope of the LV cavity signal enhancement) was used for the calculation of segmental MPRI. MPRI was defined as the ratio of relative upslope (stress) to relative upslope (rest), and segmental values were averaged. Our in-laboratory intrarater reliability for measuring MPRI, reported as a coefficient of variation, is 3.6%. Delayed enhancement images were read by an experienced investigator to identify areas of regional fibrosis.

Statistical Analysis
Baseline characteristics are presented as means±SD or proportions. Inferential data are reported as means±SE, with differences between cases and controls compared using Student t tests. Normality was assessed by the Kolmogorov–Smirnov goodness-of-fit test. Multiple linear regression analysis was performed to assess the relationship between indices of diastolic function (peak circumferential strain and peak untwisting rate) and multiple patient characteristics (ie, age, body mass index, blood pressure, LV mass, heart rate, and global MPRI). In all cases, differences were considered significant if P values <0.05.

Results
Twenty cases and 15 age-matched controls underwent cardiac MRI with contrast. Subject characteristics are presented in the Table. By design, cases and controls were well matched for age and body mass index. No group differences in resting heart rate, blood pressure, LV mass, or LV concentricity (mass/
end-diastolic volume) were found between the groups. Consistent with previous observations, 62% of the cases had a history of hypertension, although treated blood pressure was not different from the reference control group. Likewise, 62% of cases were also hyperlipidemic, and 19% had a history of type 2 diabetes mellitus. As expected, MPRI was lower in cases than in controls ($P<0.05$). We found no evidence of myocardial fibrosis (delayed enhancement) in any of the cases studied.

### Preserved LV Systolic Function
LV global systolic function (ie, LV ejection fraction) was well preserved in cases compared with controls (see the Table). Likewise, circumferential strain ($−20.7±0.6\%$ versus $−21.9±0.5\%$) and systolic circumferential strain rate ($−105.9±6.1\%$ versus $−109.0±3.8%$ per second) were also found to be similar between cases and controls.

### Impaired LV Diastolic Function
LV diastolic function was assessed in 3 ways. First, using tissue tagging, we assessed the peak rate of circumferential strain in diastole, which was found to be greatly impaired in cases versus controls (Figure 2). Second, also using tissue tagging, we assessed the peak rate of basal to apical rotation (ie, peak untwisting rate), demonstrating an impairment in cases compared with controls (Figure 2). Third, using conventional cinematic imaging, we assessed early peak filling rate. Unlike tissue tagging parameters, peak ventricular filling rate was found to be similar between cases and controls ($356.4±27.5$ versus $370.0±14.9$ mL/s).

In addition to functional parameters of LV diastolic function, we also assessed the timing of each diastolic event. Cases and controls differed significantly with regard to the timing of specific diastolic event: (1) the timing of peak filling rate was
with a group of age- and body mass index–matched controls. Our results were independent of common cardiovascular risk factors, including age, body mass index, hypertension, or LV hypertrophy.

Angina, an evidence of ischemia, in women is a major health problem, yet it remains underdiagnosed and undertreated. One possible contributing factor may be our continued over-reliance on global markers of cardiac function, such as ejection fraction or fractional shortening. It is now well established that patients presenting with symptoms of cardiac failure will often have normal LV ejection fractions. Thus, to achieve early, targeted treatment, more sensitive imaging modalities, which are capable of evaluating the entire cardiac cycle, are needed. Here, by using cardiac MR tissue tagging, we were able to detect diastolic differences in a cohort of women with signs and symptoms of ischemia but no obstructive CAD.

Cardiac MR tissue tagging provides 2 important measures of LV diastolic function: strain rate and the rate of ventricular untwisting. Diastolic strain rate reflects the rate of tissue deformation (ie, myocyte lengthening) during early diastole, similar to early myocardial tissue velocities measured by Doppler ultrasound. Unlike Doppler ultrasound, however, strain imaging provides more direct information about tissue lengthening and is less affected by the tethering of noncontracting cardiomyocytes or the Doppler insonation angle, thus making it a more superior measure of myocardial relaxation. LV untwisting occurs as a result of the left ventricle’s unique helical fiber orientation, which gives rise to basal-to-apical rotation/twisting during systole. During diastole, stored potential energy generated during systole is released as kinetic energy, resulting in early rapid ventricular untwisting. Indeed, the rate of ventricular untwisting is strongly associated with the transmirtal pressure gradient and the rate of isovolumic relaxation. The seminal finding of this investigation was that both diastolic strain rate and peak LV untwisting rate are reduced in women with signs and symptoms of ischemia but no obstructive CAD.

We also assessed the rate of early LV filling by using cinematic imaging, which is similar to conventional mitral inflow velocimetry. In our hands, this conventional technique failed to detect differences in diastolic function between cases and controls. We think that this further highlights the added benefit of using newer, more sensitive MRI techniques, such as MR tissue tagging. Interestingly, cinematic imaging was able to detect a significant diastolic time delay in patients compared with controls, suggesting that it took longer to achieve a similar peak ventricular filling rate. This finding was also confirmed by tissue tagging.

Diastolic dysfunction is multifactorial and increasingly recognized as a major contributing factor of morbidity and mortality. Factors such as cardiac hypertrophy, myocardial fibrosis, metabolic dysfunction of cardiomyocytes, or microvascular abnormalities have all been implicated. Our imaging studies ruled out cardiac hypertrophy as a major contributing mechanism because we found no difference in LV mass or LV concentricity between cases and controls. Myocardial fibrosis is also an unlikely contributing factor because none of the patients studied showed evidence of myocardial fibrosis on delayed enhancement imaging.

### Table. Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases</th>
<th>Controls</th>
<th>PValue</th>
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<tr>
<td>Calcium channel blocker</td>
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Data reported as mean±SD unless otherwise specified. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LV, left ventricular; and MPRI, myocardial perfusion reserve index.

In women with signs and symptoms of ischemia in the absence of obstructive CAD, we observed differences in diastolic function—with preserved systolic function—compared to controls. The rate of early LV filling, as assessed by cinematic imaging, was significantly reduced in cases compared with controls. We also observed differences in diastolic function, with both diastolic strain rate and peak LV untwisting rate being lower in cases compared with controls. These findings highlight the added benefit of using newer, more sensitive imaging techniques to detect diastolic dysfunction in women with ischemia but no obstructive CAD.

Lastly, we performed multiple linear regression analysis to assess whether diastolic function, measured by MR tissue tagging, was related to common cardiovascular risk factors. Diastolic circumferential strain rate and peak untwisting rate remained significantly different between groups, even after adjusting for cardiovascular risk factors (P=0.03 and 0.02, respectively). Neither diastolic circumferential strain rate nor peak untwisting rate were predicted by age, body mass index, arterial blood pressure, LV mass, LV concentricity, or resting heart rate. Moreover, diastolic dysfunction was not found to be related to MPRI.

### Discussion

In women with signs and symptoms of ischemia in the absence of obstructive CAD, we observed differences in diastolic function—with preserved systolic function—compared to controls. The rate of early LV filling, as assessed by cinematic imaging, was significantly reduced in cases compared with controls. We also observed differences in diastolic function, with both diastolic strain rate and peak LV untwisting rate being lower in cases compared with controls. These findings highlight the added benefit of using newer, more sensitive imaging techniques to detect diastolic dysfunction in women with ischemia but no obstructive CAD.

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with gadolinium. Thus, although the current experimental approach does not allow us to completely differentiate changes in relaxation from that of compliance, the general absence of hypertrophy or fibrosis strongly suggests impairments in relaxation, rather than compliance per se. We hypothesize that diastolic dysfunction is secondary to the clustering of risk factors (eg, hypertension, diabetes mellitus, obesity) commonly observed in this syndrome.

The clinical significance of our results remains unclear. Diastolic heart failure, commonly referred to as heart failure with preserved ejection fraction, is an increasingly recognized entity with similar, if not worse, clinical outcomes compared with traditional heart failure with reduced ejection fraction. Older women with ≥1 Framingham risk factors are often the group affected by heart failure with preserved ejection fraction and make up the bulk majority of our population. Indeed, we have also observed a relatively high proportion of new-onset heart failure hospitalizations and nonfatal myocardial infarctions in this population. It is, therefore, interesting to speculate that our observations provide important subclinical insight into a group of patients destined for heart failure. Perhaps early identification of cardiac abnormalities with such sensitive imaging techniques as performed here provides an important treatment window to prevent/rescue disease progression.

Limitations

Conventional Doppler ultrasound was not performed in the present investigation to assess diastolic function, which limits the clinical applicability. However, as discussed, we consider strain imaging to be a more robust measure of diastolic function. Of course, speckle-tracking echocardiography can also provide similar strain information, with similar sensitivity and variability as MRI. However, because our study also included LV morphology and myocardial perfusion measurements (where MRI is clearly superior to echocardiography),

Figure 2. MR tissue tagging reveals differences in diastolic function in women with angina who were free from obstructive coronary artery disease (cases) and a group of age- and body mass index–matched reference controls (controls). A, Circumferential strain from a representative case (solid line) and a representative control (dashed line) subject. Time 0 represents end-systole. Red dashed line illustrates differences in the rate of relaxation. B, Summary data showing significant reductions in circumferential diastolic strain rate in cases compared with controls. C, Left ventricular (LV) torsion in a representative case (solid line) and a representative control (dashed line) subject. Time 0 represents end-systole. Red dashed line illustrates differences in the rate of ventricular untwisting. D, Summary data showing significant reductions in the rate of LV untwisting in cases compared with controls. Data are reported as mean±SE.
Diastolic Dysfunction in Women With Ischemia

In conclusion, women with signs and symptoms of ischemia in the absence of obstructive CAD have abnormalities in diastolic function, as assessed by high-resolution cardiac MRI. This hypothesis-generating study provides encouraging insight into the pathophysiology of this disease and opens new opportunities for future studies to explore specific mechanisms as well as potential treatment options—both on acute effectiveness and long-term survival.

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Disclosures

None.

References


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This study used cardiac magnetic resonance tissue tagging to test the hypothesis that left ventricular diastolic function is impaired in a cohort of women with signs and symptoms of ischemia in the absence of obstructive coronary artery disease. We observed significant reductions in both diastolic circumferential strain rate and peak left ventricular untwisting rate. This is the first study to demonstrate diastolic dysfunction in women with signs and symptoms of ischemia in the absence of coronary artery disease and sets the stage for future studies to address specific mechanisms of action and evaluate potential therapeutic countermeasures.
Diastolic Dysfunction in Women With Signs and Symptoms of Ischemia in the Absence of Obstructive Coronary Artery Disease: A Hypothesis-Generating Study

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