The role of cardiac MRI in the diagnosis of women’s cardiovascular disease

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More than 400,000 women in the United States die every year from cardiovascular disease (CVD), making it the leading cause of death of women in the US [1]. Despite the advances made in the diagnosis and treatment of CVD in men, the effective diagnosis of CVD in women is limited by their atypical symptom presentation and the reduced sensitivity and specificity of diagnostic testing in women compared to men [2, 3].

Unfortunately, women with CVD also have a higher risk for cardiac events and mortality once diagnosed, increasing the need for tests that diagnose disease at an earlier or even subclinical stage. Thus, there is an urgent and unmet need for new diagnostic strategies in both asymptomatic and symptomatic women with CVD.

The landmark National Heart, Lung, and Blood Institute (NHLBI) sponsored study, Women’s Ischemic Syndrome Evaluation (WISE), made several important contributions to our understanding of CVD in women by [2, 3]:

• defining the unique pathophysiology of CVD in women;
• demonstrating that measurements of coronary vascular dysfunction in women predicted risk of future events;
• outlining the direct unmet need to diagnose women with atypical presentation of CVD.

An abridged summary of the WISE study findings is given in Table 1. To summarize the WISE study findings, women presenting with chest pain are less likely to have obstructive coronary artery disease (CAD) and more likely to have abnormalities of coronary vascular reactivity. Importantly, these abnormalities of coronary flow are tied to the risk of future cardiac events. However, these studies were based on invasive angiography in symptomatic women. Identifying a non-invasive strategy that measures coronary vascular dysfunction could be extended clinically for diagnosis and management strategies in women with non-obstructive CAD [2, 3].

The challenges of imaging women

The challenges encountered by other non-invasive diagnostic modalities highlight cardiac MRI as an ideal non-invasive imaging modality in women. In general, non-invasive modalities face the challenge of detecting disease in women who have smaller epicardial coronary arteries, lower left ventricular mass and smaller left ventricular size than men, and greater chest wall attenuation.

Specific advantages of MRI for evaluation of women include excellent soft tissue characterization and contrast, three-dimensionality, an absolute quantification of blood flow, and overall superior temporal and spatial resolution to image vascular and myocardial abnormalities. In addition, the epidemics of obesity and type 2 diabetes have lead to more women presenting with CAD during childbearing age, creating greater concern for tests involving ionizing radiation: for example, computed tomography (CT) and single photon emission computed tomography (SPECT). MRI is free from ionizing radiation thereby avoiding radiation exposure to sensitive tissues.

Current applications of cardiac MRI

During a single clinical cardiac MRI session, every diagnostic imaging need reported in the WISE study (Table 1) potentially can be met. Currently, cardiac MRI techniques are available to acquire images that can assess morphology, function, perfusion and viability. A combination of any or all of the techniques shown in Table 2 can be collected to investigate evidence of CAD and/or CVD in women.
Measurements of cardiovascular function, including ejection fraction, cardiac output, and total muscle mass, can be obtained reliably with a high degree of accuracy and in a short period of time (Figure 2). Ventricular function can be performed at rest, or under pharmacologically-induced stress, to permit assessment of silent (asymptomatic) ischemic events.

While the anatomical and functional imaging techniques discussed above have become routine for clinical cardiac MRI practice, contrast agent enhancement techniques are often acquired to provide additional information regarding cardiovascular health. Cardiac perfusion images (Figures 3 and 4) can be collected at rest and under stress during the first passage of contrast agent.

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<th>Study findings</th>
<th>Direct needs</th>
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<tr>
<td>Traditional diagnostic tests to identify obstructive disease do not work as well in women</td>
<td>Study symptoms, disabilities, and indicators that are abnormal but not a “typical” presentation</td>
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<tr>
<td>The “typical” female presentation of Ischemic Heart Disease (IHD) is more complex and multi-factorial then in men</td>
<td>Evaluate combination of symptoms, risk factors and stress-induced imaging markers to improve risk assessment</td>
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<td>There may be gender-specific response to atherosclerotic risk burden mediated by reproductive hormones</td>
<td>Further inquiry as to which functional measures should be considered “at-risk” even without obstructive CAD</td>
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<td>Signs and symptoms of IHD without obstructive coronary disease is a significant health problem for women</td>
<td>New imaging techniques that document the diagnosis of ischemia due to vascular dysfunction</td>
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<td>Estrogen deficiency in premenopausal women with presentation of IHD may be etiologic for obstructive coronary disease during postmenopausal years</td>
<td>Assess role of gender-specific reproductive hormones in IHD etiology, pathophysiology, diagnostic and prognostic assessment, and therapeutic response</td>
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<th>Technique</th>
<th>Purpose</th>
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<td>Bright blood</td>
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<tr>
<td>Black blood</td>
<td>Morphology</td>
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<tr>
<td>Cine</td>
<td>Qualitative wall motion, ventricular function</td>
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<td>Tagging</td>
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<td>Perfusion</td>
<td>Assess regional blood supply</td>
<td>Lower artifact incidence; greater spatial resolution and coverage</td>
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<tr>
<td>Coronary angiography</td>
<td>Assess vessel narrowing</td>
<td>Whole-heart coverage; greater vessel contrast</td>
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<td>Delayed enhancement</td>
<td>Myocardial viability</td>
<td>Greater scar contrast</td>
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Currently, cardiac MRI is used clinically to study CVD. Further details of these clinical studies are given in this article. The extent to which MRI can be used to diagnose CAD is under investigation. The potential for diagnosing CAD using MRI is also described in this article. A summary of these techniques follows.

For morphologic assessment, gradient echo-derived white-blood and spin echo-derived black-blood sequences are used, the latter of which removes confounding blood signals from the images to highlight the underlying morphology (Figure 1). In addition, functional cardiac MR can be used to evaluate myocardial motion by acquiring a temporal series of images.
Figure 1. 3T black-blood images. Two chamber, four chamber, and short axis views.

Figure 2. Balanced-Steady State Free Precession (bSSFP) cine images at 3T. End diastole and systole, short axis view.

Figure 3. Stressed first-pass perfusion image at 1.5T (right) shows perfusion deficit (double arrows) in myocardial tissue, in agreement with X-ray angiography findings (left).
gadolinium-based contrast agents. Delayed enhancement techniques use inversion recovery (IR) pulses to visualize the transmural extent of an infarction.

In addition to morphology, function, perfusion and viability assessment, techniques for cardiac vessel angiography, blood flow and myocardial strain measurements have been developed, although they are not used as widely in clinical cardiac MRI practice. Coronary magnetic resonance angiography (MRA) techniques that aim to visualize the coronary vessel lumen have greatly improved over the past few years and now allow artery-targeted or whole-heart coverage (Figure 5) with high spatial resolution in short scan times.

To enhance blood contrast, a T2-preparation pulse suppresses tissues with short T2 relaxation times, such as myocardium. Alternatively, an additional IR preparation in the presence of a gadolinium contrast agent can greatly improve the conspicuity of proximal and distal arteries. Coronary MRA can potentially assess the subset of women who have obstructive CAD. Phase contrast angiography (PCA) can quantify flow in major and some minor vessels surrounding the heart from the phase difference of flowing spins. The image contrast in PCA is obtained from phase subtraction of flow compensated and flow sensitive acquisitions.

Figure 4. Rest perfusion time series at 3T, collected during first-pass of bolus, allows higher spatial resolution compared to 1.5T.

Figure 5. Non-contrast RCA-targeted MRA reformatted using Soapbubble software (left) and contrast-enhanced whole-heart MRA reformatted using maximum intensity projection (right), both acquired at 3T. When contrast agent is present, the coronary veins are also visible (double arrow).

Figure 6. Grid-line tagged images at 3T. End diastole and systole, short axis view.
Myocardial tagging techniques are similar to functional imaging with the addition of gridded saturation bands or spatial modulation of the magnetization (SPAMM). Myocardial tagging traditionally has been used in cardiac research to observe and quantify wall motion abnormalities by applying material fiducial markers to the tissues with preparatory pulses (Figure 6), thereby allowing direct quantification of motion.

**Advances in cardiac MRI**

Technical advances in cardiac MRI have strengthened its case as the standard diagnostic tool for women suspected of CVD. Use of vector cardiogram (VCG) algorithms has allowed for more reliable cardiac triggering, which greatly enhances the quality of cardiac cine imaging. Improvements in real-time respiratory navigation permit longer acquisitions for whole-heart 3D image collection allowing higher spatial resolution scans [4, 5].

Cardiac-dedicated phased-array surface coils with as many as 32 elements have led to increased signal to noise ratio (SNR) and reduced scan time using higher acceleration rates [6]. Further improvements in spatiotemporal resolution appear likely from incorporation of novel k-space sampling strategies (for example, k-t BLAST, k-t SENSE) [7]. The “autoviability” technique (Figure 7) uses phase-sensitive inversion-recovery (PSIR) viability imaging to extend the nulling point dynamic range, and thus reduces the dependence on an exact inversion time for delayed enhancement imaging [8].

Lastly and possibly most valuable, the move to a higher static magnetic field with significant increase in SNR and contrast to noise ratio (CNR) has presented an opportunity to increase the utility of cardiac MRI for diagnosis of CVD in women [9-12]. Specifically, vasodilator stress myocardial perfusion imaging and whole-heart coronary MR angiography at 3T have advantages over 1.5T.

The theoretical doubling of SNR can be traded for higher spatial resolution, greater heart coverage with high temporal resolution or shorter scan times, and an increase in vascular SNR and CNR with the addition of T1-shortening contrast agents. A recent study has shown that the dark-rim artifact observed in first-pass cardiac perfusion studies, which can be mistaken for perfusion deficit, occurs more at 1.5T (23%) than 3T (8%) even with equal spatial resolution acquisition [9].

Previously, steady-state free-precession imaging sequences had been restricted to 1.5T due to increased static field non-homogeneities at 3T. Recent technological advances in localized shimming correct the static magnetic field and allowed these techniques to be utilized at 3T, harnessing their ability to double the overall SNR of the acquisition [13]. Table 2 outlines the current cardiac MRI techniques and the possible benefits of 3T for each technique.

**Future directions for cardiac MRI for non-obstructive CAD assessment**

Impairment of coronary vasoreactivity may appear before the development of obstructive lesions, and coronary endothelial dysfunction potentially can be observed before structural changes are appreciated by angiography [2]. Invasive measurements of coronary flow reserve are predictive of events for women and patients with angina without obstructive coronary lesions [14, 15]. The ability to non-invasively assess coronary vasoreactivity would be particularly important in the diagnosis and treatment of women as an early marker of subclinical atherosclerosis [16-18]. Stress-induced changes in coronary function and blood flow velocity using high-resolution cardiac function and PCA techniques (Figure 8) may indicate the presence of endothelial dysfunction.

Myocardial perfusion imaging is clinically established for hemodynamic assessment of obstructive epicardial stenosis. Additionally, these images help detect perfusion abnormalities that occur only under stress conditions and help to better understand the role of microvascular hypoperfusion in detecting CVD without obstructive CAD.

Importantly, an MR perfusion imaging study by Panting et al. [19] showed that subendocardial ischemia may be responsible for chest pain in women with angina without obstructive CAD. Myocardial perfusion reserve, which can be assessed by comparing stress versus non-stress MR perfusion measurements, is inversely associated with cardiac risk factors and coronary artery calcium in asymptomatic individuals, including patients with non-obstructive CAD [20]. In a similar fashion, this technique may offer a non-invasive assessment of coronary vasoreactivity in asymptomatic individuals at high risk for coronary artery disease.

The WISE study reported that changes in the myocardial high-energy phosphates, phosphocreatine and adenosine triphosphate, from rest to pharmacologically-induced stress might be a marker of CVD without evidence of CAD [3]. In fact, a decrease in phosphocreatine/
adenosine triphosphate ratio during stress indicated a shift toward anaerobic metabolism (in other words, myocardial ischemia) in 20% of women with chest pain without obstructive CAD.

Furthermore, at three-year follow-up, women with a decreased phosphocreatine/adenosine triphosphate ratio during stress at initial examination demonstrated a rate equal to women with obstructive CAD. New developments in cardiac multi-nuclear MR spectroscopy, in particular 31P imaging, are capable of measuring these changes and may potentially be included in a clinical cardiac MR protocol to assess women with possibility of CVD, with and without obstructive CAD [3].

As asymptomatic and symptomatic cardiovascular disease in women becomes better understood, there is a greater need for non-invasive techniques to diagnose non-obstructive coronary artery disease (CAD). Cardiac magnetic resonance has a complete spectrum of tools to assess cardiac morphology, function, perfusion, viability and coronary vascular dysfunction in a single clinical study.

Figure 7. Short-axis PSIR delayed enhancement images at 3T. Mid slice (left) shows infarcted myocardium (arrows) that is not present in a basal slice (right) of the same short-axis image stack.

Figure 8. Flow quantification images of the right coronary artery (arrows) acquired at 3T – phase (top) and magnitude (bottom).

There is a greater need for non-invasive techniques to diagnose non-obstructive CAD.
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References


