

A new cardiac variable identified?

Mark Doyle

Allegheny General Hospital, Pittsburgh, PA, USA

Corresponding to: Mark Doyle, PhD. Division of Cardiology, CV MRI Center, Allegheny General Hospital, 320 East North Avenue, Pittsburgh, PA, 15212-4772, USA. Email: mdoyle@wpahs.org.

Abstract: Women with suspected cardiac syndrome X (CSX) are difficult to diagnosis and treat by conventional means. The women's ischemic syndrome evaluation (WISE) study, which started as an exploration of ischemic heart disease, increasingly focused on CSX, and two papers that represent an outgrowth and extension of this work are featured in this issue. Cardiovascular magnetic resonance imaging (CMRI) can generate a myocardial perfusion reserve index (MPRI) that is shown to be lower in women with CSX compared to normal controls. The MPRI is a ratio of resting to vasodilatation myocardial perfusion uptake and is relatively easy to measure. There is growing evidence that the CMRI measured MPRI provides unique information that should be regarded as a primary indicator of CSX disease severity. The papers describe the low levels of MPRI in a well documented CSX all female patient population. The context of this work and its relationship to other findings is discussed with an emphasis on the unique information that CMRI can provide.

Key Words: Cardiovascular; magnetic resonance imaging (MRI); cardiac syndrome X (CSX); myocardial perfusion reserve index (MPRI)



Submitted Sep 07, 2013. Accepted for publication Sep 10, 2013.

doi: 10.3978/j.issn.2223-3652.2013.09.02

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Women with suspected cardiac syndrome X (CSX) lack a widely accepted path to diagnosis and treatment (diagnosis being largely one of exclusion). The word “syndrome” indicates a collection of symptoms and conditions associated with a disease process that do not well conform to a paradigm that what we hold to be true. In 1999, the women's ischemic syndrome evaluation (WISE) study sought to develop a novel non-invasive diagnostic means of assessing ischemic heart disease (IHD) in women (1). This took the concept of the “syndrome” one step further, specifically applying it to women who tend to have less specific presentation of disease symptoms *vs.* men (2). Some have questioned the legitimacy of the designation of “syndrome” with regard to IHD in women *vs.* men, speculating that differences might be a matter of perception (3). However, when careful examinations of disease severity, treatment and outcomes of women *vs.* men were conducted, a preponderance of evidence demonstrated worse outcomes for women (4). While the WISE study was established to

investigate a syndrome within a syndrome, there was also taciturn acknowledgement of the conventional paradigm of IHD, since initially coronary artery angiography was regarded as the gold standard for the presence of disease. During the initial WISE study, no non-invasive modality proved to outperform all others in the ability to assess ischemic heart disease when using angiography as the gold standard (5). In part, this failure was due to the relatively high incidence of CSX in the exclusively female population, rendering conventional coronary angiography an ineffective gold standard.

A thread that ran through the initial WISE study and many subsequent investigations has been the potentially novel role of cardiovascular magnetic resonance imaging (CMRI). In the clinical community, the adoption rate of CMRI has been very low, in large part because it fails to provide unique information and is generally more expensive than existing non-invasive modalities. For instance, (I) magnetic resonance angiography of the coronary

arteries does not approach the resolution and ease of acquisition associated with coronary computed tomography angiography (CCTA), (II) the CMRI acquisition of data to assess cardiac function is typically acquired over several cardiac cycles with a temporal resolution on the order of 50 ms, whereas echocardiography can acquire cardiac functional data in real time with a temporal resolution on the order of 10 ms, and (III) while CMRI perfusion assessment has generally been found to be superior *vs.* nuclear SPECT for assessing myocardial regions at risk of ischemia and in assessing the extent of non-viable tissue, in part due to increased resolution (6) nevertheless, the perceived benefits of CMRI *vs.* SPECT have not resulted in widespread replacement of SPECT with CMRI. Further, myocardial perfusion assessment by either CMRI or SPECT may be soon superseded by sending patients from the Emergency Department directly to CCTA for assessment of their coronary arteries (7). However, the straight to CCTA solution does not challenge the IHD paradigm, whereas a new paradigm may be needed.

To place CMRI in its correct role in evaluation of CSX, it may be necessary to step away from the guiding paradigm and look at the evidence in a new light. Instead of looking at how well CMRI compares to other imaging modalities, it may be instructive to consider what unique information CMRI provides. By definition, a unique variable does not strongly correlate with any other variable. Two related papers in this edition consider the role of CMRI-measured myocardial perfusion reserve index (MPRI) in women without obstructive coronary artery disease, who nevertheless experience angina. In the first paper (Agarwal *et al.*; Cardiac risk factors and myocardial perfusion reserve in women with microvascular coronary dysfunction), the CMR-measured MPRI was calculated as the relative response in signal uptake between resting and vasodilatation conditions and was shown to only loosely correlate with risk factors for IHD. The second paper (Shufelt *et al.*; Cardiac magnetic resonance imaging MPRI assessment in women with microvascular coronary dysfunction and reference controls) compares the CMR-measured MPRI in women with CSX *vs.* a normal control group (matched on several variables, but with evidence of IHD). All the women suspected of CSX exhibited some abnormality in coronary reactivity testing (CRT) measured at the cath lab. This paper shows that the CSX patients had a lower MPRI *vs.* controls, indicating that the CMR-measured MPRI is an entity associated with CSX. However, what CMRI designates as MPRI and what the cath lab identifies as an

abnormal CRT are derived from quite different quantities: signal intensity in the case of CMRI and coronary flow and diameter changes in the case of the cath lab (8). While we might expect some relationship between the two measures, there are multiple variables that influence each measurement and calculation, (including the provocative agents used in CMRI *vs.* the cath lab (globally administered adenosine *vs.* regionally administered nitroglycerine, acetylcholine and adenosine, respectively) lessening the expectation that they will be identical.

One referenced paper sought to carefully eliminate assumptions in the CMRI measure of MPRI and derive, via sophisticated data modeling, an absolute measure of myocardial blood perfusion (9). They showed that there was no difference in absolute blood perfusion in controls *vs.* CSX patients. Again, we note that the relatively simple measure of CFR by CMR is removed by several steps from the calculation of absolute delivery of blood perfusion, and should be regarded as a measurement in its own right. Further, the definition of what comprises a CSX patient differed between publications.

The studies presented here did not address outcomes, but other papers in the same strain have looked at these issues and found that CMR provides unique information that has a high prognostic value. In one of the early WISE publications, it was noted that women with an inadequate CMRI-measured MPRI exhibited poor agreement between myocardial perfusion status and the cath lab, whereas those with an adequate MPRI exhibited better agreement between perfusion status and the cath lab (10). This pattern of agreement with the cath lab was noted for both CMRI and nuclear SPECT and was not too surprising, since the premise of the vasodilatation perfusion test is to produce a state of hyperemic blood flow, and failure to achieve an adequate MPRI meant that the patient did not experience any significant change in blood flow between the resting and vasodilatation scans. Importantly, the ability to assess MPRI status was only measurable by CMRI. No correlates with blood pressure or change in heart rate were found to allow SPECT to assess the validity of the examination. An inadequate MPRI was observed in about 30% of patients, indicating that 30% of SPECT examinations were substandard but that no parameter was available to alert the physician to this situation. Having a diagnostic test that is only applicable in 70% of patients is disappointing, but not knowing which patients are adequately tested is a serious deficiency. Considering that much of the information concerning CSX patients comes from clinical observation,

and historically the dominant modality that guided the clinical path was SPECT (11), the adequacy of the MPRI response becomes a key issue. Outside of carefully controlled studies, there is a great danger that clinical data may bias the evidence that we use to form our guiding paradigm.

In another instance using the WISE population, a global myocardial perfusion index was shown to have good prognostic value in women with low levels of coronary artery stenoses (<50%) (12). Again, this was a measurement and calculation that was unique to CMRI, with no correlate in nuclear SPECT or the cath lab noted. Importantly, it also showed that severe adverse cardiovascular events were associated with patients with low levels of epicardial coronary artery disease. This high event rate is illustrative of the extent to which our guiding paradigm for CSX may be biased (13), but it is supportive of the growing evidence demonstrating the non-benign nature of CSX (14). We note that in situations where CMRI and SPECT measure the same entity, such as left ventricular volume, the prognostic value of each modality is similar (15).

Investigations into conditions such as CSX may be doubly prejudiced since we measure what we believe and preferentially weight in importance evidence that fits our paradigm, subtly or overtly rejecting unfavorable results. When the data shows that there are only loose correlates between modalities, and after we are satisfied that this low correlation is not a function of measurement inaccuracy, then perhaps we should begin to regard the variable as unique and not be surprised if it turns out to be the missing variable that explains more of the symptoms and events than conventional variables. Adopting this course necessitates a move away from the paradigm focusing on flow-limiting coronary artery disease, and even away from conventional measures of CFR. The CMRI-measured CFR is emerging as a unique parameter not directly assessable to other modalities, which is preferentially present in women with CSX and has been shown to have prognostic value.

Acknowledgements

Disclosure: The author declares no conflict of interest.

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Cite this article as: Doyle M. A new cardiac variable identified? *Cardiovasc Diagn Ther* 2013;3(3):118-121. doi: 10.3978/j.issn.2223-3652.2013.09.02