

# Diagnosing Ischemia With Vasodilatory Stress Cardiac Magnetic Resonance: The Benefit of a Comprehensive Approach

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Cardiac magnetic resonance (CMR) has developed into a powerful and unparalleled non-invasive technique for the evaluation of cardiovascular disease. Besides optimal structure definition, it provides some tissue characterization and simultaneous information about cardiac function and viability. Furthermore, in combination with a pharmacological challenge using vasodilator or inotropic drugs, CMR has the capability to diagnose ischemia. Stress CMR is increasingly used for the diagnosis and evaluation of myocardial ischemia and viability, providing a safe and effective evaluation of patients with coronary artery disease (CAD).<sup>1</sup>

When compared with other well-established diagnostic techniques, such as dobutamine stress echocardiography,<sup>2</sup> single-photon emission tomography,<sup>3</sup> or positron emission tomography,<sup>4</sup> stress CMR offers excellent border delineation, depiction of wall motion and a high spatial resolution without patient exposure to ionizing radiation.<sup>5</sup>

Stress CMR for the diagnosis of coronary artery disease can be performed using 2 different techniques: *a*) stress perfusion CMR, which tests the presence of inducible myocardial perfusion defects during administration of a vasodilator stimulus, usually adenosine or dipyridamole; and *b*) imaging of wall motion abnormalities, usually performed during dobutamine infusion.<sup>6</sup>

Stress perfusion CMR is intended to detect perfusion defects through the downstream microvascular blood flow within the myocardium<sup>7</sup> while imaging of inducible wall motion abnormalities

aims to detect the physiological response of the cardiac muscle to that aggression, a latter stage of the ischemic cascade. These differences may have a significant impact in terms of sensitivity and specificity for coronary artery disease detection and should be considered for management optimization.<sup>8,9</sup>

Adenosine and dipyridamole are the most commonly used stressors during CMR perfusion. They act as coronary vasodilators, inducing near-maximal coronary vasodilation primarily through activation of adenosine receptors in vascular smooth muscle. This global hyperaemia of the coronary vascular beds is independent of metabolic demand and allows detection of perfusion defects in the areas supplied by stenotic vessels.<sup>10</sup> Dobutamine is generally used in stress CMR for detection of ischemia-induced wall motion abnormalities. It induces true ischemia through an increase in the work-load, mimetizing physiological stress.<sup>9,11</sup>

However, the vasodilator properties of dobutamine as well as the capability of the vasodilators (adenosine and dipyridamole) to induce wall motion abnormalities may also be used for diagnostic optimization and several stress CMR studies have studied the added value of this combined approach.<sup>12-14</sup>

The diagnostic performance of stress CMR has been tested by several clinical studies and a recent meta-analysis examined the results of the published studies on stress CMR both for perfusion and for wall motion abnormalities.<sup>5</sup> Furthermore, multicenter clinical trials have been published for CMR perfusion.<sup>15,16</sup>

According to the current appropriateness criteria for cardiac magnetic resonance imaging, the use of both CMR perfusion and dobutamine stress CMR imaging is indicated for the diagnosis of ischemia in patients complaining of chest pain and with an intermediate pre-test probability of CAD, in whom the ECG is uninterpretable or who are unable to exercise. Furthermore, stress CMR is indicated as post-test assessment in patients already examined with invasive or computed tomography coronary angiography showing coronary lesions of unclear functional significance.<sup>17</sup>

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In a very interesting study published in this issue of *Revista Española de Cardiología*,<sup>18</sup> Husser et al tested the additional diagnostic value of inducible abnormal wall motion for the detection of coronary artery disease during dipyridamole stress perfusion CMR.

From a total population of 600 patients who underwent dipyridamole stress perfusion CMR, 166 patients who also underwent coronary angiography were studied for the potential diagnostic benefit of adding cine sequences during the dipyridamole infusion CMR protocol for the evaluation of inducible abnormal wall motion.

In this retrospective single centre study, the authors studied the presence of first-pass perfusion deficits and of inducible abnormal wall motion under dipyridamole CMR perfusion and correlated those parameters with the presence of CAD (defined as presence of stenosis  $\geq 70\%$  assessed by the coronary angiography). As expected, the authors found that both the presence of perfusion deficit and of inducible abnormal wall motion were independently related to CAD. In accordance with previous published works,<sup>9,12,29</sup> the authors also found that perfusion imaging had a higher sensitivity but a lower specificity for the detection of coronary artery disease when compared to inducible wall motion abnormalities (WMA). When compared with patients with stress perfusion deficits only, patients with inducible WMA were found to represent a more diseased population in terms of CAD (more hypoperfused segments and more diseased vessels). This correlates well with the concept of the ischaemic cascade with a higher grade of ischaemia required for the induction of abnormal wall motion when compared to perfusion defects, which occur at an earlier level of the cascade.

Despite the limitations that result from the retrospective nature of the study, with implications in the interpretation and generalization of the results, due to a “verification bias” (that tends to overestimate sensitivity and underestimate specificity of the test), the findings suggest an important added value of imaging wall motion during stress as a complement to perfusion imaging. The additional information about inducible WMA can be obtained in a very short period of time (during a 14 seconds breath-hold), making this approach easily applicable in clinical practice.

One of the major advances of this study is that it confirms the benefit of a comprehensive CMR approach for the diagnosis of CAD, using a different pharmacological stressor. For the first time, the diagnostic benefit of adding sequences for detection of inducible abnormal wall motion during dipyridamole stress CMR was studied. Similar to what was found during adenosine CMR perfusion,<sup>12</sup> inducible WMA with dipyridamole mainly occur in

high grade epicardial stenoses ( $>75\%$ ). According to the authors, the high specificity of inducible abnormal wall motion might balance out the lack of specificity of perfusion data.<sup>18</sup> Although this may be true from a purely academic perspective, in current clinical practice it only increases the predictive value for CAD in those cases where inducible WMA are seen; it cannot rule out CAD when no inducible abnormal wall motion is found (sensitivity of only 43% in this already biased population). Thus, its addition to the standard perfusion protocol would not significantly change patient management after the test: patients with positive perfusion scans would most likely be referred for invasive angiography independently of the wall motion evaluation. However, we could speculate that patients with induced WMA, which have more severe coronary disease, represent the group of patients that would benefit most from a coronary intervention. In the light of the COURAGE trial<sup>20</sup> we know that current practice may be over-diagnosing and over-treating coronary artery disease. This way, the “lower sensitivity” for the detection of dipyridamole-induced WMA may, in fact, be advantageous for an optimal decision-making, as it could better identify the proposed “ischemic threshold” above which revascularization would be superior to medical therapy.<sup>21,22</sup> This hypothesis would merit further investigation and this alternative management strategy would need to be studied in a prospective prognostic trial. Another interesting aspect would be to understand if, despite of its lower sensitivity and its later occurrence in the ischemic cascade, evaluation of inducible abnormal wall motion is able to detect any case of CAD that would not be detected if only perfusion results were used (2 patients with inducible abnormal wall motion (4%) had a normal perfusion scan). In that case, the addition of the cine sequence could be justified for all perfusion cases, since this 14 seconds duration breath-hold could change clinical management. However, this cannot be deduced from the data presented.

Previous works<sup>12,14</sup> focused on the combined use of perfusion and wall motion imaging with CMR for the detection of CAD. Taking together, these studies show that the combination of sequences adds some diagnostic value to either technique alone. If we add the additional diagnostic and prognostic value of scar imaging with late gadolinium enhancement technique in this context,<sup>23,24</sup> we may find CMR to be one of the best and most comprehensive approaches for the non-invasive diagnosis of coronary artery disease. No other method is capable to give similarly precise information about perfusion defects, induced wall motion abnormalities and scar, all of which are

predictors of CAD. Differently from other studies<sup>23</sup> the delayed enhancement index used in this study was not an independent predictor of CAD and therefore it was not incorporated in the multivariate model to predict CAD. By the contrary, and in line with the findings already described, the addition of inducible abnormal wall motion to perfusion data and gender information improved the C-statistic of this model.

The authors conclude that detection of inducible abnormal wall motion along with perfusion imaging offers additional diagnostic value for detecting CAD and allows identification of patients with severe ischemia and a high probability of CAD. Even though this additional value might be relatively small, since it can be obtained during the same stress test, takes only 15 seconds to obtain, may allow to grade the severity of ischemia, and may identify those patients who are most likely to profit from revascularization, it seems worthwhile to routinely acquire this data during stress examinations.

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