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## Imaging the Physiology of the Ischemic Cascade:

### Are 2 Tools Better Than 1?

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Stress cine function and vasodilating stress perfusion are commonly used approaches for the evaluation of ischemic heart disease. Both imaging approaches, using either stress echocardiography or stress nuclear scintigraphy, have stood the test of time as highly accurate in diagnosing coronary artery stenosis and as prognostic tools in patients with symptoms suspicious of myocardial ischemia.<sup>1,2</sup> When epicardial coronary flow is interrupted and leads to an imbalance between myocardial oxygen supply and demand, reduced myocardial perfusion, regional ventricular dysfunction, and ECG change occur in quick succession; hence, the term “ischemic cascade” has been described.<sup>3</sup> This phenomenon has been well described after acute balloon inflation during percutaneous coronary intervention and also during demand ischemia induced by dobutamine stress. Consequently, capturing abnormalities of both perfusion and function, in an attempt to improve the diagnostic performance of noninvasive tests, has been the focus of investigation using echocardiography and nuclear scintigraphy, with encouraging results.<sup>4–6</sup>

In this issue of *Circulation: Cardiovascular Imaging*, Gebker et al<sup>7</sup> described the diagnostic utility of cardiac MRI (CMR) for evaluation of coronary artery disease using both myocardial perfusion (DSMRP) and function (DSMR) assessments during high-dose dobutamine stress testing. As shown in their work, CMR has technical features that are well suited for imaging both perfusion and regional function during a single, high-dose dobutamine infusion. With advances in imaging speed and algorithms of accelerated data reconstruction, gated cine steady-state free precession imaging can capture regional left ventricular dysfunction from ischemia at high temporal resolution and contrast-to-noise ratio. At target heart rates during peak stress, first-pass perfusion can sample myocardial blood flow across multiple slice locations at high frequency, without the need to interrupt the dobutamine infusion. In addition, all cine function, perfusion, and late enhancement imaging can be acquired with reproducible and matching slice locations. This study represents one of the largest experiences to date on stress CMR in assessing coronary artery disease. The authors should be commended for their effort in conducting this study, with >91% of the 455 patients achieving diagnostic-quality study and reaching target heart rates. When DSMRP was included in the diagnostic criteria, it increased the test sensitivity from 85% to 91% (versus DSMR alone;  $P=0.001$ ) in detecting angiographic coronary stenosis of 70% luminal narrowing. Of the 150 patients without evidence of ischemia by DSMR, 19 (13%) were correctly detected to have inducible ischemia by DSMRP when compared with angiographic luminal stenosis of 70%. These findings are consistent with the current understanding of coronary pathophysiology. Factors such as collateral circulations, effects of antianginal medications, number and severity of diseased coronary arteries, and concurrent use of atropine for heart rate augmentation will influence the development of myocardial ischemia during dobutamine challenge. Common to all forms of stress cine wall

motion imaging, test sensitivity is limited because of the need to induce sustained ischemia from which contractile dysfunction will eventually manifest.<sup>8</sup> In a canine model of myocardial ischemia, Leong-Poi et al<sup>9</sup> reported that perfusion abnormalities preceded and involved a larger myocardial extent than worsened regional function during demand ischemia. It is therefore not surprising that Gebker et al<sup>7</sup> demonstrated enhanced diagnostic sensitivity with the addition of myocardial perfusion. This finding is further supported by the high proportion of single-vessel coronary artery disease (59% of all patients with angiographic coronary artery disease) in their patient population in whom the spatiotemporal discordance between perfusion and cine functional abnormality during stress was expected to be intensified.

The authors, however, reported that the overall improved sensitivity by the addition of DSMRP comes at a cost of a reduced test specificity (from 82% to 70%) in detecting a luminal stenosis of 70%, which led to no improvement of the overall diagnostic accuracy gauged by the Youden index. A number of issues need to be considered before the results of Gebker et al can truly represent the diagnostic utility of dobutamine stress CMR. First, their reported test specificity is low and is not consistent with stress CMR reports in the literature, including a recent multicenter study.<sup>10-12</sup> Technical issues may be a factor leading to a higher rate of false-positive DSMRP findings. As shown in Figure 1 of the article by Gebker et al<sup>7</sup>, DSMRP was acquired at every other cardiac cycle when the target heart rate was achieved at peak dobutamine infusion. As a result, motion blurring and inadequate temporal resolution may lead to artifacts perceived as perfusion defects, therefore increasing the false-positive ratio. The use of steady-state free precession DSMRP for data readout and high acceleration by parallel imaging technique (sensitivity encoding factor 3.0 used in 1.5 T) are also known to contribute to image artifacts and reduced image quality of CMR myocardial perfusion imaging.<sup>13,14</sup> Second, significant spectrum bias (or referral bias) existed in this patient population because all patients had an established decision to proceed to coronary angiography at the time of CMR enrollment. The specific reasons to proceed to angiography were not provided but, the effects of this bias were evidenced by a high prevalence of coronary stenosis on angiography (69% and 76% for 70% and 50% luminal stenosis, respectively). It is therefore unclear whether the high false-positive rate by DSMRP as presented by Gebker et al will remain the same when dobutamine stress CMR is called for assessing more common patients with an intermediate pretest likelihood of disease. Third, qualitative grading of a solitary coronary lesion as 70% or <70% luminal narrowing is far from a sound clinical reference standard. None of the factors for coronary flow impediments from sequential lesions, outward vessel wall remodeling, diffuse distal tapering, or endothelial dysfunction, which all lead to reduced myocardial perfusion, can be accounted for by this method of stenosis grading. In the presence of such high prevalence of coronary artery disease in this patient cohort, a false-positive DSMRP defect may represent a true finding of relative reduction of regional myocardial perfusion.

With the advent of hardware and software improvements, CMR myocardial perfusion technique has achieved very high image quality during recent years across all major MRI vendors. It has been shown that dobutamine infusion at an intermediate stage, when the target heart rate is not yet reached, can provide adequate vasodilatation of the coronary bed.<sup>15</sup> From a technical standpoint, acquisition of DSMRP at this intermediate dobutamine stage will lessen the potential for artifacts and blurring as a result of the high heart rates during peak dobutamine stress and may improve the test specificity. Interpretation of CMR myocardial perfusion can be either qualitative or quantitative. Compared with regional contractile dysfunction, quantitative perfusion analysis may provide an assessment less influenced by observer bias and experience.<sup>16</sup> Potential drawbacks of a combined DSMR and DSMRP study exist. First, the inclusion of DSMRP leads to additional costs of the study. Second, at least in some patients, the clinician will be faced with the challenge of

making clinical decisions based on conflicting results from DSMRP and DSMP. A predefined plan of weighing the risks and benefits of the different management options must be made before performing combination studies. Third, although a growing body of clinical evidence suggests that vasodilator stress CMR myocardial perfusion can impact prognosis in patients in whom a negative test result portends to a favorable 2-year cardiac outcome,<sup>17,18</sup> whether such prognostic value can be maintained in DSMRP independent of DSMR is currently unknown and will need to be addressed by a future prospective study. Fourth, as the current study is not powered to draw conclusions from subgroup analysis, future studies will have to address which patient groups can benefit most from the diagnostic information of a combined CMR approach. Nonetheless, the results from Gebker et al reflect a clinical experience in which important lessons have been learned and provide encouraging evidence in the role of comprehensive characterization of myocardial physiology possible by CMR.

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