

EDITORIAL COMMENT

Does Dobutamine Stress Perfusion Imaging Solve the Riddle of Ischemia in LBBB?*

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In patients with an intermediate likelihood for the presence of coronary artery disease (CAD), most of today's guidelines require proof of myocardial ischemia before invasive angiography. Similarly, significant myocardial ischemia should be demonstrated before revascularization. The most recent European Society of Cardiology guidelines for patients with stable coronary artery disease leave the choice of the test to the practitioner on the basis of local expertise (1). The recently published multimodality appropriateness criteria for detection and risk assessment in stable ischemic heart disease have rated various imaging modalities on the basis of existing evidence, assuming they are equally available with appropriate quality and expertise, while suggesting to keep cost-effectiveness and value in mind when ordering such tests (2).

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Direct comparisons between different imaging modalities are rare, as patients have to undergo both imaging modalities as well as an invasive reference standard to allow for a direct and unbiased comparison. Most studies so far have been comparing adenosine stress perfusion with cardiac magnetic resonance (CMR) and single-photon emission computed tomography as the latter is the most frequently performed test in patients with stable CAD but is burdened by radiation and low spatial

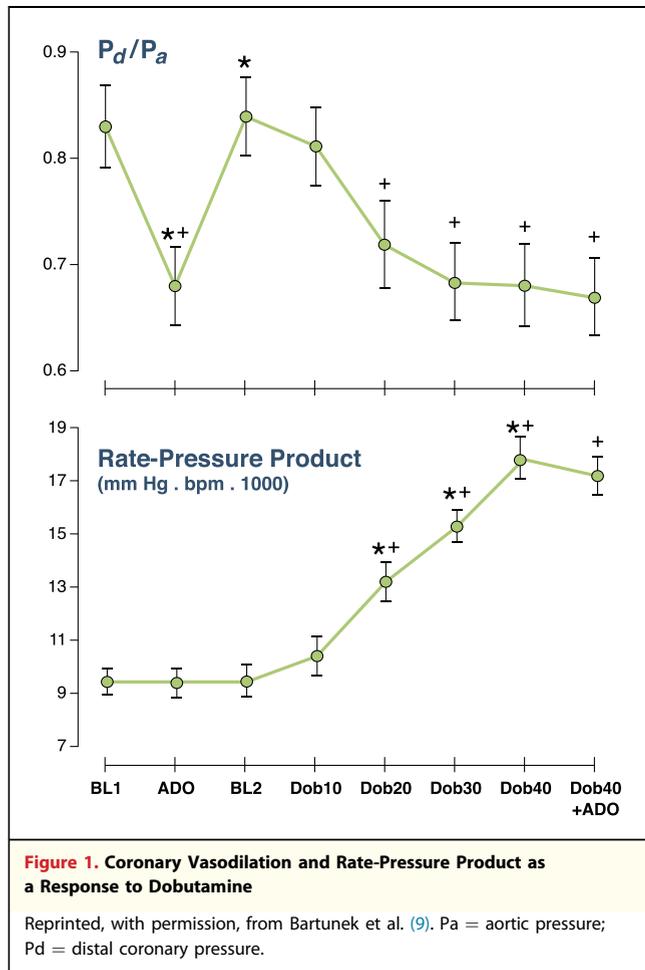
resolution. Results have demonstrated noninferiority or superiority of CMR to single-photon emission computed tomography (3,4).

Less data is available for the comparison of dobutamine stress cardiac magnetic resonance (DSCMR) and dobutamine stress echocardiography (DSE) even though DSE is among the most frequently used tests in stable chest pain patients, especially in Europe. In an early study in 1999, Nagel et al. (5) demonstrated a superior diagnostic accuracy for DSCMR versus DSE to detect significant CAD; however, the methods used no longer reflect today's state-of-the-art echocardiography or CMR technology. In addition, there are no data on specific subgroups such as patients with left bundle branch block (LBBB), which pose specific challenges on noninvasive imaging due to their asynchronous myocardial motion and thickening.

In this issue of *JACC*, Mordi et al. (6) provide a comparison of contrast-enhanced DSE with DSCMR and invasive angiography in 82 patients with LBBB. In addition to high-dose dobutamine wall motion imaging, they assessed first-pass perfusion during an intermediate dose of dobutamine (20 µg dobutamine/kg body weight/min) and the presence of scar tissue by late gadolinium enhancement (LGE) CMR. They found similar sensitivity (70.6%) and a tendency toward higher specificity of DSCMR wall motion imaging in comparison to DSE (87.5% vs. 72.9%), with a resultant tendency for better accuracy (80.4% vs. 72.0%). This is further improved by adding perfusion imaging at 20 µg dobutamine/kg body weight and LGE. Thus, in patients with LBBB, a "comprehensive CMR" examination that includes dobutamine stress wall motion, first-pass perfusion imaging at an intermediate dobutamine dose, and LGE appears to be an excellent test to detect significant CAD and seems to overcome some of

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the limitations that methods which rely only on wall motion (DSCMR and particularly DSE) have in this population.

The paper by Mordi et al. (6) provides important answers and closes a knowledge gap on which imaging modality to use in this important and difficult subgroup of patients. However, further important questions are also raised.

What Is the Best Dose for Dobutamine Stress Perfusion Imaging?

It is interesting that perfusion imaging improved specificity but reduced sensitivity in comparison to wall motion imaging. On the basis of the ischemic cascade, one would expect a higher sensitivity of perfusion imaging as perfusion defect occurs earlier than wall motion abnormalities do. In addition, inducible wall motion abnormalities usually occur in areas with transmural or significant endocardial perfusion defects. Previous studies adding perfusion imaging to wall motion assessment have also rather demonstrated an increased sensitivity, both for CMR

(7) as well as for echocardiography (8). In some studies, a lower specificity was observed when adding perfusion analysis to the diagnostic workup (7).

A possible explanation for this observation is the use of 20 μg dobutamine/kg body weight/min in the current study, whereas most studies so far have proposed perfusion imaging at peak dose to achieve maximal vasodilation. In an invasive study, Bartunek et al. (9) have assessed coronary pressure during various doses of dobutamine. They found significant vasodilation at 20 μg dobutamine with some (but not statistically significant) additional dilation at 30 μg dobutamine (Fig. 1). Additional infusion of adenosine did not lead to further vasodilation. From the original data, one may argue that a dose of 30 μg may slightly improve sensitivity due to the increased vasodilation. At the same time, higher heart rates can decrease image quality of CMR perfusion imaging, potentially leading to a lower specificity. Although the answer to this question cannot be found in the current data, the dose proposed by Mordi et al. (6) appears to add value to the stress examination and was safe and feasible. Lastly, the effect on sensitivity and specificity of any stress test is also influenced by the criteria used to denote CAD. The comprehensive CMR examination in the current study (6) yielded optimal results when using a perfusion defect in a region of induced wall motion abnormality (as opposed to either finding) to increase specificity or scar by LGE with or without additional ischemia to increase sensitivity in patients with LBBB. However, the observed LGE pattern in the studied group was typical of CAD in all patients. Further experience is needed to validate these observations in the larger clinical setting, particularly in patients with a mixed scar pattern.

Should Perfusion Always Be Added to Wall Motion Assessment?

Whereas early studies did not demonstrate superior or additional value of perfusion imaging to wall motion assessment (10), this has changed in recent years. Most likely this is due to the improved methodology used for perfusion imaging resulting in high quality datasets with high spatial resolution. Falcão et al. (8) nicely demonstrated the added value of perfusion imaging to both modalities, echocardiography as well as CMR, for improved sensitivity. The value of reversible perfusion abnormalities (and LGE) will likely be even more important in patients with LBBB and depressed left ventricular function. In the study by Mordi et al. (6), the population had intermediate risk for coronary disease, and we

suspect ventricular function was preserved overall (but no assessment was provided). The difficulties of assessing CAD in the presence of LBBB are compounded in patients with depressed ventricular function, where cardiomyopathy and/or coexistent CAD may be important. More studies are needed to evaluate the relative value of each component of wall motion, perfusion, and LGE in ischemia detection and their impact in a less select population with LBBB.

What Is the Correct Reference Standard?

Obviously any study in patients with CAD today is challenged by the lack of an optimal reference standard. While we understand that fractional flow reserve downgrades many stenoses deemed hemodynamically significant by invasive angiography, the correlation of FFR with ischemic burden or the ischemic burden relevant to patients' symptoms and prognosis are largely unknown. By using a 70% cutoff value for significance of a stenosis, the investigators avoided having too many "false negative" noninvasive tests in patients with stenosis but no or only small

areas of ischemia. However, the accuracy of the CMR study was measured against an anatomical test and as such may not reflect a truly better performance. In a recent publication, Shaw et al. have summarized criteria for different imaging modalities to assess ischemic burden and provided some first estimate on the predictive value of different severities of myocardial ischemia. Studies such as the ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) trial or the MR-INFORM (MR Perfusion Imaging to Guide Management of Patients With Stable Coronary Artery Disease) study (11) will provide a better understanding on the impact of ischemia on outcome. Once such data is available, we will also be able to better define a reference standard against which to measure "superiority."

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REFERENCES

1. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. *Eur Heart J* 2012;33:1787–847.
2. Wolk MJ, Bailey SR, Doherty JU, et al. ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2014;63:380–406.
3. Schwitzer J, Wacker CM, Wilke N, et al., for the MR-IMPACT Investigators. MR-IMPACT II: Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary Artery Disease Trial: perfusion-cardiac magnetic resonance vs. single-photon emission computed tomography for the detection of coronary artery disease: a comparative multicentre, multivendor trial. *Eur Heart J* 2013;34:775–81.
4. Greenwood JP, Maredia N, Younger JF, et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. *Lancet* 2012;379:453–60.
5. Nagel E, Lehmkuhl HB, Bocksch W, et al. Noninvasive diagnosis of ischemia-induced wall motion abnormalities with the use of high-dose dobutamine stress MRI: comparison with dobutamine stress echocardiography. *Circulation* 1999;99:763–70.
6. Mordi I, Stanton T, Carrick D, et al. Comprehensive dobutamine stress CMR versus echocardiography in LBBB and suspected coronary artery disease. *J Am Coll Cardiol Img* 2014;7:490–8.
7. Gebker R, Jahnke C, Manka R, et al. Additional value of myocardial perfusion imaging during dobutamine stress magnetic resonance for the assessment of coronary artery disease. *Circ Cardiovasc Imaging* 2008;1:122–30.
8. Falcão SN, Rochitte CE, Junior WM, et al. Incremental value of perfusion over wall-motion abnormalities with the use of dobutamine-atropine stress myocardial contrast echocardiography and magnetic resonance imaging for detecting coronary artery disease. *Echocardiography* 2012;30:45–54.
9. Bartunek J, Wijns W, Heyndrickx GR, de Bruyne B. Effects of dobutamine on coronary stenosis physiology and morphology: comparison with intracoronary adenosine. *Circulation* 1999;100:243–9.
10. Paetsch I, Jahnke C, Wahl A, et al. Comparison of dobutamine stress magnetic resonance, adenosine stress magnetic resonance, and adenosine stress magnetic resonance perfusion. *Circulation* 2004;110:835–42.
11. Hussain ST, Paul M, Plein S, et al. Design and rationale of the MR-INFORM study: stress perfusion cardiovascular magnetic resonance imaging to guide the management of patients with stable coronary artery disease. *J Cardiovasc Magn Reson* 2012;14:65.

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