Myocardial perfusion reserve index during adenosine stress magnetic resonance for the detection of coronary artery disease - ready for prime time?

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J Thorac Dis 2013;5(3):362-363. doi: 10.3978/j.issn.2072-1439.2013.04.04

In the work recently published in *Cardiovascular Diagnosis and Therapy*, Goykhman *et al.* (1) evaluated the inter- and intra-observer variability of myocardial perfusion reserve indexes (MPRI) during first-pass perfusion cardiovascular magnetic resonance (CMR). Studies were conducted on 20 adenosine stress studies of 10 female patients with stable angina and 10 healthy volunteers. Data analysis was performed using a commercially available software tool. The authors found that variations are present in measurement of MPRI observed in post processing of perfusion data. This may affect the diagnosis of inducible perfusion abnormalities and therefore the diagnostic classification and risk stratification of patients with suspected or known ischemic heart disease.

During the last 2 decades, first-pass perfusion cardiovascular magnetic resonance (CMR) underwent a multitude of changes and developments including improved hardware, software, and contrast agents, all aiming at better understanding of the mechanisms of contrast enhancement. Myocardial perfusion imaging by first-pass contrast enhanced CMR was introduced by Atkinson *et al.* in 1990, who first used an inversion recovery gradient echo pulse sequence during the injection of Gd-DTPA, successfully visualizing contrast agent transit through the LV cavity and the heart muscle on CMR images (2). Subsequently, myocardial perfusion imaging has undergone continuous development both in terms of technical improvements (better gradient systems, higher magnetic field strength, improved radiofrequency coil arrays and pulse sequence design and refined perfusion analysis methods) and in terms of experimental validation, and clinical evaluation. In this regard, evaluation included numerous preclinical animal models of ischemic heart disease (3,4), as well as clinical studies (5-7). Although earlier CMR studies had limitations, such as poor slice coverage and low temporal resolution, limiting the detection of CAD, subsequent data demonstrated that CMR compares favorably to SPECT for the detection of regional myocardial ischemia (8-10). In a recent prospective, real world clinical trial, which included 752 consecutive patients, CMR exhibited significantly higher diagnostic accuracy compared to SPECT for the detection of anatomically significant CAD (11). Due to the lack of radiation exposure for the patients, its higher spatial resolution and its versatility to assess myocardial function, perfusion and if required viability during a single examination, CMR is considered to date as the first choice technique for the diagnostic work-up of patients with ischemic heart disease. Therefore, the assessment of inter- and intra-observer variability of MPRI by contrast enhanced CMR as assessed in the present manuscript by Goykhman *et al.* is a very important goal, because such variability may significantly affect the diagnosis of CAD.

In the clinical routine most CMR centers perform visual analysis of perfusion scans for the diagnosis of inducible ischemia during pharmacologic hyperemia with adenosine or dypiridamole. With visual analysis, the transmural extent of a perfusion deficit is determined from the single dynamic image showing the maximum extent of regional hypoenhancement. Hereby, increase in regional hypoenhancement during adenosine stress (≥25% increase in hypoenhancement transmurality compared to baseline scans) in at least one myocardial segment, which persists for ≥5 consecutive image frames, is considered as indicative of inducible ischemia (12). With semi-quantitative analysis on the other hand, regions of interest are defined in the LV cavity and in myocardial segments and spatially averaged signal intensity values are used to plot signal intensity curves over time in the myocardial circumference and in the center of the LV blood pool. Hereby, the mean signal intensity prior to contrast agent injection is subtracted from all post-contrast data, and the maximum upslope of the resulting signal intensity time curves is determined by using a linear fit, based on the least-squares regression line. By this approach, a myocardial perfusion reserve

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Submitted Mar 05, 2013. Accepted for publication Apr 03, 2013.
Available at www.jthoracdis.com

ISSN: 2072-1439

index is calculated by dividing the corrected upslope at pharmacologic hyperemia through the corrected upslope at rest, which serves as a semi-quantitative estimate of the myocardial perfusion reserve. This procedure involves several steps which are operator dependent, including: (I) manual contouring of the LV circumference, (II) manual contour adjustment for e.g., due to patient breathing and (III) manual definition of the starting and the ending points of the signal intensity curves. All these steps may be conducted differently by different observers, which results in variability of the resultant MRPI measures. In their study, Goykhman *et al.* meticulously studied the inter- and intra-observer variability of such measures. They found an inter-observer intra-class correlation coefficient (ICC) of 0.80 (95% CI, 0.57-0.92) with a coefficient of variation (CoV) of 7.5%, and an intra-observer ICC of 0.89 (95% CI, 0.77-0.95) with a CoV of 3.6%. The mid-ventricular level MPRI was most reproducible, with an intra-observer ICC of 0.91 (95% CI, 0.77-0.97), whereas intra-observer measurements were generally more reproducible than inter-observer measurements. In the same line, a recent study by Larghat & Plein *et al.*, reported inter-observer CoV of 4-10% for the assessment of MPRI, which is acceptable for diagnostic use. However, when perfusion studies were repeated the inter-study CoV were significantly higher (13-27%) (13). In the same study, semi-quantitative analysis by MPRI was more reproducible than the quantitative analysis of absolute myocardial blood flow (MBF) estimated using Fermi-constrained deconvolution. Slightly higher CoV (9% for inter-observer and 5.3% for intra-observer measurements) were recently reported by Chih *et al.* (14), using the Philips View Forum workstation. This may be attributed to different image quality in the 2 studies and the presence of multi-vessel symptomatic coronary artery disease in most patients of the latter study (14).

The work of Goykhman *et al.* constitutes a further step forward for the implementation of semi-quantitative myocardial perfusion reserve index estimates in the diagnostic work-up of patients with ischemic heart disease. Now, further studies are warranted in order to investigate to what extent the reported variability in MPRI can affect the diagnostic classification and risk stratification of patients undergoing contrast enhanced stress CMR. From a technical point of view software MR manufacturers are now called to develop and refine algorithms for the automatic segmentation of the LV myocardium, in order to further reduce variability in MPRI measurements, possibly increasing the robustness of this novel technique for CAD detection.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Korosoglou G, Katus HA. Myocardial perfusion reserve index during adenosine stress magnetic resonance for the detection of coronary artery disease - ready for prime time? J Thorac Dis 2013;5(3):362-363. doi: 10.3978/j.issn.2072-1439.2013.04.04