Variability in quantitative cardiac magnetic resonance perfusion analysis

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ABSTRACT

By taking advantage of its high spatial resolution, noninvasive and nontoxic nature first-pass perfusion cardiovascular magnetic resonance (CMR) has rendered an indispensable tool for the noninvasive detection of reversible myocardial ischemia. A potential advantage of perfusion CMR is its ability to quantitatively assess perfusion reserve within a myocardial segment, as expressed semi- quantitatively by myocardial perfusion reserve index (MPRI) and fully- quantitatively by absolute myocardial blood flow (MBF). In contrast to the high accuracy and reliability of CMR in evaluating cardiac function and volumes, perfusion CMR is adversely affected by multiple potential reasons during data acquisition as well as post-processing. Various image acquisition techniques, various contrast agents and doses as well as variable blood flow at rest as well as variable reactions to stress all influence the acquired data. Mechanisms underlying the variability in perfusion CMR post processing, as well as their clinical significance, are yet to be fully elucidated. The development of a universal, reproducible, accurate and easily applicable tool in CMR perfusion analysis remains a challenge and will substantially enforce the role of perfusion CMR in improving clinical care.

KEY WORDS Stress cardiac magnetic resonance (CMR) imaging; quantitative analysis; reproducibility

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In the past two decades, first-pass perfusion cardiovascular magnetic resonance (CMR) has rendered an indispensable tool for the noninvasive detection of reversible myocardial ischemia. By taking advantage of its high spatial resolution, noninvasive and nontoxic nature CMR perfusion imaging has achieved an improvement in sensitivity and specificity for the detection of coronary artery disease (CAD) (1) and has given further insights into the understanding of ischemic heart disease.

CMR perfusion imaging has been validated against more established invasive, catheter-based (2) as well as other noninvasive imaging modalities [echocardiography (3), single-photon emission computed tomography (SPECT) (4,5), and positron emission tomography (PET)] (6). Ongoing technical innovation with the development of improved hardware, software and novel technical approaches, such as novel spatial-temporal acceleration techniques (7,8), introduction of novel contrast media (9), and blood oxygen-level dependent contrast (10) have improved the exam's diagnostic performance for the assessment of coronary artery status and myocardial ischemic burden and offered the potential to being employed as a clinical endpoint. In this respect, it is now readily available for routine clinical assessment of CAD patients.

A potential advantage of perfusion CMR is its ability to quantify perfusion reserve within a myocardial segment. Although time-demanding, compared to visual interpretation, quantitative evaluation of myocardial perfusion properties with CMR, as expressed semi- quantitatively by myocardial perfusion reserve index (MPRI) (11) and fully- quantitatively by absolute myocardial blood flow (MBF) (12), may provide additional clinically relevant information and an objective, stepwise correlation of myocardial perfusion impairment to the severity of coronary artery status.

A semi-quantitative analysis of myocardial perfusion is based on the assessment of the signal-intensity changes over the course of the first pass of the contrast through the myocardium. The upslope integral technique has been the most effective semi-quantitative method that was studied and yields a high diagnostic

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accuracy in patients with suspected CAD (1). The accuracy of the upslope analysis may, however, be affected by differences in the contrast agent's pharmacodynamics and pharmacokinetic properties. The use of fully quantitative perfusion analysis helps to avoid these problems. Techniques such as Fermi function deconvolution (13) and dual-bolus contrast administration (14) offer a relatively accurate correlation with myocardial blood flow and yield absolute MBF values, without sacrificing the contrast-to-noise ratio and subsequent image quality.

There is limited published data available for the reproducibility of serial myocardial perfusion CMR. Muhling *et al*. primarily reported good intra- and inter-observer agreement for good quality images, using semi-quantitative analysis in 14 rest and 3 stress adenosine perfusion exams (15). More recently, Morton *et al*. evaluated the inter-study reproducibility of segmental and global absolute quantitative CMR and the influence of diurnal variation on perfusion, by applying perfusion imaging three times during a single day in eleven healthy volunteers. Inter-study reproducibility was moderate, and best for global rest perfusion. No significant diurnal variation in perfusion was observed (16). In another study aiming in healthy volunteers, Larghat *et al*. assessed the reproducibility of semi-quantitative and quantitative analysis of first-pass perfusion CMR in healthy volunteers (17). Although they showed good results, reproducibility was affected by variations between intra-observer, inter-observer, and inter-study comparisons. Semi-quantitative analysis was more reproducible than quantitative analysis. Reproducibility of systolic and diastolic phases and the endocardial and epicardial myocardial layer was similar on both semi-quantitative and quantitative analysis. In parallel, as part of Multi-Ethnic Study of Atherosclerosis, the inter-study reproducibility of quantitative CMR perfusion was assessed. Although the interval between the two exams was very long (mean 334 days), interestingly this study also demonstrated reasonable inter-study reproducibility, with global and rest perfusion to be the most reproducible (18).

These findings did not differ significantly when perfusion CMR reproducibility had been examined in patients with CAD. Elkington *et al*. showed good inter-study reproducibility for segmental and global semi-quantitative and quantitative analysis in a cohort of 9 CAD patients and 7 healthy volunteers who underwent adenosine stress perfusion CMR. Reproducibility was good in both patients with and without CAD, and more significant for global versus regional analyses (19). Chih *et al*. examined the inter-study and inter-observer reproducibility of adenosine stress CMR in patients with symptomatic multi-vessel CAD and low risk for CAD. Myocardial perfusion was evaluated qualitatively by assessing the number of ischemic segments and semi-quantitatively. MPRI was lower in patients with CAD compared to those with low risk. Inter-study and inter-observer reproducibility for MPRI were high. No significant difference in reproducibility was found between patients with CAD and those with low risk CAD (20).

In the December 2012 issue of *Cardiovascular Diagnosis and Therapy*, Goykhman *et al*. (21) studied retrospectively the inter- and intra-observer reliability of the data generated by standard commercially available software for calculation of the MPRI. Stress CMR was performed using a standardized protocol in 20 women including 10 women with angina and the absence of obstructive CAD and 10 healthy volunteers. Basal, mid, and apical segments, for the whole myocardium, sub-endocardium, and sub-epicardium were analyzed. The MPRI results by repeated software measurements were highly correlated, with potentially important variations in measurement observed. The mid-ventricular level MPRI was most reproducible. Intra-observer measurement was more reproducible than inter-observer measurement.

The authors conclude that there is measurement variation inherent in the post processing of the perfusion CMR data using standard commercially available software. This variation is potentially attributed to a combination of factors including variation in stress test response, image acquisition/quality, and variation in measurements at the time of post processing.

In contrast to the high accuracy and reliability of CMR in evaluating cardiac function and volumes, perfusion CMR is adversely affected by multiple potential reasons during data acquisition as well as post-processing. Various image acquisition techniques, variation in SA slice acquisitions due to different patient positioning and breath holding, various contrast agents and doses, such as dual bolus administration as well as variable blood flow at rest as well as variable reactions to stress will all influence the acquired data. Postprocessing requires motion compensation, the detection of endo- and epicardial contours, the determination of an input function, as well as deconvolution of the myocardial response, all of which will reduce reproducibility of perfusion imaging (not only with CMR). Reproducibility may also differ due to inherent pitfalls, such as differences in the expertise between centers.

Mechanisms underlying the variability in perfusion CMR post processing, as well as their clinical significance, are yet to be fully elucidated. Nonetheless, post- processing variation reflects the practical challenges encountered in both clinical practice and research. No quantitative perfusion analysis technique has been adopted in clinical practice at this time, and visual inspection performed by an experienced reporter remains the mainstay of clinical reporting. An approach to standardize interpretation and post-processing on CMR studies is needed. The development of a universal, reproducible, accurate and easily applicable tool in CMR perfusion analysis remains a challenge and will substantially enforce the role of perfusion CMR in improving clinical care.

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References

1. Nagel E, Klein C, Paetsch I, et al. Magnetic resonance perfusion measurements for the noninvasive detection of coronary artery disease. Circulation 2003;108:432-7.
2. Costa MA, Shoemaker S, Futamatsu H, et al. Quantitative magnetic resonance perfusion imaging detects anatomic and physiologic coronary artery disease as measured by coronary angiography and fractional flow reserve. J Am Coll Cardiol 2007;50:514-22.
3. Arnold JR, Karamitsos TD, Pegg TJ, et al. Adenosine stress myocardial contrast echocardiography for the detection of coronary artery disease: a comparison with coronary angiography and cardiac magnetic resonance. JACC Cardiovasc Imaging 2010;3:934-43.
4. Schwitter J, Wacker CM, van Rossum AC, et al. MR-IMPACT: comparison of perfusion-cardiac magnetic resonance with single-photon emission computed tomography for the detection of coronary artery disease in a multicentre, multivendor, randomized trial. Eur Heart J 2008;29:480-9.
5. 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.
6. Morton G, Chiribiri A, Ishida M, et al. Quantification of absolute myocardial perfusion in patients with coronary artery disease: comparison between cardiovascular magnetic resonance and positron emission tomography. J Am Coll Cardiol 2012;60:1546-55.
7. Morton G, Ishida M, Schuster A, et al. Perfusion cardiovascular magnetic resonance: Comparison of an advanced, high-resolution and a standard sequence. J Cardiovasc Magn Reson 2012;14:34.
8. Jogiya R, Kozerke S, Morton G, et al. Validation of dynamic 3-dimensional whole heart magnetic resonance myocardial perfusion imaging against fractional flow reserve for the detection of significant coronary artery disease. J Am Coll Cardiol 2012;60:756-65.
9. Schroeder MA, Clarke K, Neubauer S, et al. Hyperpolarized magnetic resonance: a novel technique for the in vivo assessment of cardiovascular disease. Circulation 2011;124:1580-94.
10. Karamitsos TD, Leccisotti L, Arnold JR, et al. Relationship between regional myocardial oxygenation and perfusion in patients with coronary artery disease: insights from cardiovascular magnetic resonance and positron emission tomography. Circ Cardiovasc Imaging 2010;3:32-40.
11. Al-Saadi N, Nagel E, Gross M, et al. Noninvasive detection of myocardial ischemia from perfusion reserve based on cardiovascular magnetic resonance. Circulation 2000;101:1379-83.
12. Hsu LY, Groves DW, Aletras AH, et al. A quantitative pixel-wise measurement of myocardial blood flow by contrast-enhanced first-pass CMR perfusion imaging: microsphere validation in dogs and feasibility study in humans. JACC Cardiovasc Imaging 2012;5:154-66.
13. Jerosch-Herold M, Wilke N, Stillman AE. Magnetic resonance quantification of the myocardial perfusion reserve with a Fermi function model for constrained deconvolution. Med Phys 1998;25:73-84.
14. Ishida M, Schuster A, Morton G, et al. Development of a universal dual-bolus injection scheme for the quantitative assessment of myocardial perfusion cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2011;13:28.
15. Mühling OM, Dickson ME, Zenovich A, et al. Quantitative magnetic resonance first-pass perfusion analysis: inter- and intraobserver agreement. J Cardiovasc Magn Reson 2001;3:247-56.
16. Morton G, Jogiya R, Plein S, et al. Quantitative cardiovascular magnetic resonance perfusion imaging: inter-study reproducibility. Eur Heart J Cardiovasc Imaging 2012;13:954-60.
17. Larghat AM, Maredia N, Biglands J, et al. Reproducibility of first-pass cardiovascular magnetic resonance myocardial perfusion. J Magn Reson Imaging 2013;37:865-74.
18. Jerosch-Herold M, Vazquez G, Wang L, et al. Variability of myocardial blood flow measurements by magnetic resonance imaging in the multi-ethnic study of atherosclerosis. Invest Radiol 2008;43:155-61.
19. Elkington AG, Gatehouse PD, Ablitt NA, et al. Interstudy reproducibility of quantitative perfusion cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2005;7:815-22.
20. Chih S, Macdonald PS, Feneley MP, et al. Reproducibility of adenosine stress cardiovascular magnetic resonance in multi-vessel symptomatic coronary artery disease. J Cardiovasc Magn Reson 2010;12:42.
21. Goykhman P, Mehta PK, Agarwal M, et al. Reproducibility of myocardial perfusion reserve - variations in measurements from post processing using commercially available software. Cardiovasc Diagn Ther 2012;2:268-77.

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