Going with the flow: how reproducible are cardiac magnetic resonance measurements of myocardial perfusion?

John Biglands, Sven Plein

Multidisciplinary Cardiovascular Research Centre & The Division of Cardiovascular and Diabetes Research, Leeds Institute of Genetics, Health & Therapeutics, University of Leeds, Leeds, UK

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Myocardial perfusion imaging using cardiac magnetic resonance (CMR) is becoming a widely used clinical tool. With the recent publication of large scale clinical trials providing evidence for its high diagnostic accuracy in coronary heart disease, there is a growing evidential basis for CMR based perfusion measurements as an alternative to the most commonly used method, Single Photon Emission Computer Tomography (1,2). Clinically, CMR perfusion images are usually interpreted visually. This however introduces subjectivity to the analysis and so quantitative and semi-quantitative measurements have been devised to allow more objective assessments of myocardial blood flow. Such measurements may prove to be important for diagnosing coronary heart disease, especially in the case of multiple vessel disease, where the lack of healthy reference myocardium can render visual assessment unreliable.

Fully quantitative analysis aims to provide absolute measures of blood flow but is challenging in practice, not least due to additional requirements for data acquisition and time-consuming post-processing (3). For these reasons quantitative measurements, although increasingly used in research, are not commonly implemented in commercial software packages or used in clinical practice. More commonly incorporated into post-processing packages are so-called "semi-quantitative" analysis methods. These use characteristics of the signal-intensity (SI) profiles of first pass perfusion studies such as the maximal upslope of the SI profile to derive an index of perfusion. This is a less ambitious undertaking than fully quantitative analysis and its appeal lies in its relative simplicity compared with quantitative analysis.

Corresponding to: Professor Sven Plein. Multidisciplinary Cardiovascular Research Centre & The Division of Cardiovascular and Diabetes Research, Leeds Institute of Genetics, Health & Therapeutics, University of Leeds, Leeds, LS2 9JT, UK. Email: s.plein@leeds.ac.uk.

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A study by *Goykhman et al.*, (4) published in *Cardiovascular Diagnosis and Therapy* is concerned with the reproducibility of semi-quantitative measurements as generated by one particular commercially available software system (CAAS MRV 3.3 software, Pie Medical Imaging B.V., Netherlands). Published reproducibility studies for quantitative and semi-quantitative perfusion in CMR are sparse and so the paper is of some relevance to the field. In 20 subjects, notably all female, the authors measured reproducibility of the myocardial perfusion reserve index (MPRI), defined as the ratio of the upslopes of the SI profiles of stress versus rest perfusion studies. They report low inter-observer variability with a coefficient of variability (CoV) of 7.5% and an intra-class correlation coefficient (ICC) of 0.80. Intra-observer reproducibility was also low with a CoV of 3.6% and ICC of 0.91. These results compare favourably with a previous similar study by *Chih et al.* (5) and the authors suggest that differences in analysis software and image quality may be responsible for the improvement. Two other relevant studies are surprisingly not cited in the current paper. *Larghat* and colleagues (6) reported an inter-observer CoV 8.6-9.6% and intra-observer CoV 4.5-5.4% for MPRI, analysed separately for systolic and diastolic myocardial phases. A study by *Muhling et al.*, (7) also found inter-observer ICC 0.83 and an intra-observer reproducibility ICC 0.80. In addition, these two papers also compared semi-quantitative and quantitative reproducibility scores and found contradictory results, with *Muhling et al.*, finding a higher reproducibility in quantitative results and *Larghat et al.*, reporting the opposite.

There are a number of potential reasons for the difference in inter/intra-observer reproducibility scores between studies. As well as differences in the details of the analysis software implementation, differences in the MR imaging sequence and myocardial contouring strategy will contribute to the reproducibility, as the authors point out. Furthermore, the non-linearity between the concentration of contrast agent and the measured signal intensity in the MR image (so called saturation effects) can have a profound effect on the arterial input function (AIF) and even the myocardial response curve (8) under

certain conditions and so contrast agent bolus concentration and injection protocol will also affect reproducibility. Generally, reproducibility can be improved by adopting a standardized methodology for CMR perfusion imaging, including a consensus on imaging sequence, contrast agent injection protocol and analysis technique. Efforts are currently being made within the community to attempt to establish such a standard. In terms of data analysis, automation of myocardial contouring and analysis parameters for semi-quantitative or quantitative analysis will have a significant role to play in improving both inter/intra-observer reproducibility and inter-study reproducibility and this is an active area of ongoing research.

The current paper has a number of limitations, some of which are pointed out by the authors. The study is limited to a single software analysis system and a comparison of reproducibility scores between a range of software systems available would have been a more significant contribution. Even within the current study it would have been interesting to assess the separate contributions of the myocardial contouring and semi-quantitative analysis steps to help pinpoint the area that most contributes to reducing reproducibility. Inter-study reproducibility was not assessed in the present study. Again, the literature is sparse but inter-study reproducibility in CMR perfusion has been shown to be significantly worse than inter-observer reproducibility, at least in part due to physiological variation (6,9,10). Finally, the second figure unintentionally highlights some of the pitfalls of perfusion analysis: the endocardial contours in the figure are positioned partly within the blood pool so that myocardial data will be contaminated with blood pool signal. This is reflected in the corresponding SI profiles by a subtle upward shift of the myocardial signal as contrast arrives in the LV cavity. The SI profiles also show myocardial signal enhancing before LV signal in some segments, suggesting a partial volume effect from right ventricular blood pool in the interventricular septum. These apparent errors in contour placement will only have a small effect on the measurement of the upslope as used in this study, but they demonstrate that analysis of perfusion data requires rigorous standardization.

In conclusion, this study adds to the existing evidence showing that semi-quantitative analysis of perfusion CMR is reproducible. As the field moves towards fully quantitative perfusion estimates and increased standardization and automation of the data acquisition and analysis pipeline, reproducibility scores in such studies should improve along with inter-study reproducibility scores.

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