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How to do Quantitative Myocardial Perfusion CMR

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Prof Gerald Maurer
Editor in Chief
European Heart Journal Cardiovascular Imaging

Dear Professor Maurer

Thank you for inviting us to submit a revised draft of our manuscript entitled, "How to perform quantitative myocardial perfusion CMR" to European Heart Journal Cardiovascular Imaging. We appreciate the time and effort you and each of the reviewers have dedicated to providing insightful feedback on ways to strengthen our paper. Thus, it is with great pleasure that we resubmit our article for further consideration. We have incorporated changes that reflect the detailed suggestions you and the reviewers have provided. We hope that our edits and the responses we provide below satisfactorily address all the issues and concerns you and the reviewers have noted.

To facilitate your review of our revisions, the following is a point-by-point response to the questions and comments delivered in your letter dated 10 March 2021.

Once again, we are grateful to be given the opportunity to resubmit our manuscript.

Your sincerely,

Sven Plein and co-authors

Reviewer 1 comments:

Reviewer #1: The authors provide a brief guide on how to perform stress perfusion CMR. This brief document touches an many relevant topics including general principles of CMR perfusion, contrast agent dose, motion correction interpretation of quantitative perfusion, integration of quantitative perfusion into clinical reports, automated conversion of images to quantitative perfusion maps, and clinical evidence for quantitative perfusion CMR.

The authors present 3 potential advantages of quantitative perfusion in the early part of the paper: 1) removal of operator dependence, 2) simpler and faster analysis, and 3) the ability to detect disease with a global rather than regional reduction of MBF. Unfortunately, they never directly address any of these important concepts.

This is a complicated topic, and 5 references does not do justice to the complexity of the field. More importantly, there is almost no evidence provided to guide the reader in understanding why they came to the conclusions they did.
The presentation of two approaches to interpreting quantitative perfusion by CMR are interesting but incomplete and completely lacking a quoted evidence base. Please see specific comments on Figure

Response: We thank the reviewer for their important suggestions. While we fully agree with the reviewer on the complexity of the topic, we have submitted this paper to the 'How to" category which allows only 1500 words and 5 references. Consistent with journal guidance for this category (https://academic.oup.com/ehjcimaging/pages/General_Instructions#How-To-Articles), the aim of the manuscript is ***not*** to give a comprehensive overview of quantitative perfusion CMR, but a guide to how it is currently performed and potentially applied. While we agree with all the reviewer comments, we cannot comply with all the excellent suggestions due to the constraints of this manuscript category.

In recognition of the comments, our revision is focussed even more on practical points and less on clinical evidence. We have included this sentence in the revision to explain this more clearly: "This 'How to' article gives a brief practical overview of the steps involved in generating quantitative MBF maps and suggests how these may be used in clinical practice. This article is not intended as an exhaustive review of the principles or clinical evidence, which have been summarised elsewhere (1)". We hope that this addresses the reviewer's concerns but would be more than happy to follow any further specific suggestions to improve clarity of the scope of this paper.

Specific comments.

1. Page 4 of 12. "Dual sequence imaging is easier to integrate into clinical workflows but requires specialist scanner software." This statement is incorrect. As of the current date, there is no software approved by regulatory agencies in the EU or the US that integrates dual sequence imaging into clinical workflows. The Siemens work-in-progress software was removed from further support over two years ago. A US NIH based dual sequence program was only available through a research agreement mechanism known as "C2P" and limited to the Siemens platform. Research versions of dual sequence acquisition software appear on the Philips and GE platforms. To the best of this reviewer's knowledge, the methods remain research sequences that require research agreements.

Response: Acknowledged and reworded: "Once available outside of research settings, the dual sequence method is likely to integrate better into clinical workflow than the dual bolus method."

2. Page 5 of 12. Respiratory motion correction. There is no rigid body motion correction scheme that can adequately deal with free breathing stress perfusion acquisitions. The authors need to add an acknowledgement that non-rigid deformation methods can distort the anatomy of the heart and may

introduce other artifacts that were not present on the individual raw perfusion images. Thus, it is important for clinicians to review both raw images and parametric maps produced by these methods.

Response: Thank you for pointing this out. Motion compensation schemes are successfully integrated into Siemens, Philips, and post processing QP methods to deal with free breathing, but we acknowledge that non-rigid motion compensation can lead to artefacts and that clinical review of all data is needed. We have added this sentence: "As all motion correction methods can introduce artefacts, clinicians should always review both raw and motion corrected images."

3. Page 5 of 12. Modelling - the section must have references added.

Response: Unfortunately, due to the limit of 5 references we cannot add all the relevant references. Instead, we have quoted the most recent technical review article for further reading:

Quinaglia T, Jerosch-Herold M, Coelho-Filho OR. State-of-the-Art Quantitative Assessment of Myocardial Ischemia by Stress Perfusion Cardiac Magnetic Resonance. Magn Reson Imaging Clin N Am. 2019 Aug;27(3):491-505

4. Page 5. Verification of adequate stress. The section is also in need of references. There are several papers that suggest symptoms and heart rate response are inadequate metrics of an adequate vasodilator response. The splenic switch-off should only be recommended if referenced properly and if acknowledgement of imperfect sensitivity and specificity are added.

Response: As above, we are limited to 5 references, but in recognition of the reviewer comment have added the following:

Manisty C, Ripley DP, Herrey AS et al. Splenic switch-off: a tool to assess stress adequacy in adenosine perfusion cardiac imaging. Radiology 2015;276(3):732–740

We have also reworded the discussion of haemodynamic response and splenic-switch off, but due to the tight word count have been unable to discuss the topic in more detail. We hope to have included the key information in this sentence:

Verification of adequate stress is typically achieved by reviewing the patient's symptoms (flushing, breathlessness, and chest tightness), heart rate response (rise of ≥ 10bpm), systolic blood pressure (fall of >10mmHg) during the study and splenic switch-off on the acquired stress-images (2). However, this should not be used in isolation, and certain patient groups, particularly heart failure patients, may have a blunted haemodynamic response."

5. Page 5 of 12. The central issue for quantitative stress perfusion is the "…current lack of evidence for quantitative analysis against the wealth of evidence for visual read." Again, this is a place where references to the published literature are key on both sides of the formula.

Response: We are unable to add more references but have been much more explicit in the text on the limited evidence available for QP.

6. Figure 1A. Regional abnormal perfusion as evident on a raw perfusion image with a low quality MBF map needs to be considered a true positive perfusion abnormality and an unsuccessful MBF map. This should be an infarct or ischemia, not consider artifact. The visual interpretation of perfusion images remains the gold standard and artefactual parametric maps cannot override that existing clinical experience.

Response: We agree and have revised the figure entirely to focus on much narrower indications for QP.

7. Figure 1B. The authors need to rethink the Consider artifact category in figure 1B also. If the stress MBF map does not match the raw perfusion image, there are multiple possibilities beyond simply an artifact. The MBF map could be wrong and the perfusion image clinically correct (case 1 ischemia+/- infarct or case 2 no ischemia or infarct). The MBF map could be correct but the perfusion image misleadingly incorrect (case 3 ischemia+/-infarct or case 4 no ischemia or infarct. Ultimately, it is possible for either the MBF map or the perfusion image being true positive, false negative, true negative, or false positive. Finally, both the MBF map and the perfusion image may point in the same direction, but the extent of disease may appear quite different. This situation tends to favour the quantitative perfusion maps but several published papers suggest that the current inline perfusion tool as an issue with specificity and thus may have a tendency toward over-estimating the
extent of disease. At the same time, there are publications that suggest the visual interpretation can underestimate the extent of disease. Again, conscientious references to the literature would help modulate the presentation of a method that the authors acknowledge is not as well validated as the visual interpretation of CMR stress perfusion.

Response: We agree and have redrafted the figure entirely. Once again, we are unable to add any more references due to the limit of 5 references.

8. Reference 5 raises questions about the quantitative perfusion methods. Event rates quoted in that reference are approximately 4% versus 2% after 800 days in those with lower than median MPR and 3% versus 2% in those with lower than median stress MBF. While statistically significant, the actual discrimination of patients destined to events was rather underwhelming by either metric since there were almost the same number of subjects in each group - 1 or 2% differences.

Response: We have removed this section.

9. No diagnostic accuracy or patient management references are presented. Why should the quantitative maps change clinicians' approach to diagnosing and managing coronary artery disease? Prognosis references are more of scientific interest rather than clinical? Physicians need to know diagnostic accuracy statistics and how this alters management of patients.

Response: This is a 'How to' article, which by journal guidance is not intended to provide an in-depth review of diagnostic accuracy, prognosis etc. Instead, we are giving examples of when QP may be clinically helpful. We hope the reviewer finds these less contentious.

"There are no current guidelines on how to integrate quantitative myocardial perfusion CMR into clinical reporting and on how to combine it with visual analysis. As the bulk of the existing evidence for myocardial perfusion CMR is for visual analysis, this should continue to form the principal analysis strategy. Quantitative perfusion maps may supplement visual interpretation in several ways.

1. Confirmation of visual read: Successive or simultaneous visual and quantitative analysis may enhance diagnostic certainty where the two strategies agree and, when results are discrepant, may alert the reader to the presence of artefacts.
2. Adequacy of haemodynamic response: When inadequate haemodynamic response is suspected based on a lack of clinical response or absence of splenic switch off, review of quantitative perfusion maps can help confirm (low stress MBF and/or MPR) or refute (high stress MBF and/or MPR) this suspicion.
3. Suspected Coronary Microvascular Dysfunction (CMD): Visual interpretation of myocardial perfusion CMR has limited ability to detect CMD. In patients with no regional visual perfusion defects and adequate haemodynamic response, but low stress MBF or MPR on quantitative myocardial perfusion mapping, CMD is a likely diagnosis. Thresholds for diagnosing CMD with

quantitative myocardial perfusion CMR have been proposed in small studies but have not been widely validated and may not be applicable across different acquisition methods (3).

4. Disease extent: Visual read of myocardial perfusion CMR compares signal changes between different myocardial regions and is thus adjusted for the lowest perfused area in an image, potentially masking less severe defects elsewhere. Quantitative analysis provides objective absolute blood flow values for each region. This may be advantageous in multi-vessel CAD, where quantitative myocardial perfusion CMR may better identify disease extent than visual read (4).
5. Follow up studies and research: Quantitative myocardial perfusion CMR provides absolute numbers of MBF, which can help assess treatment effects.

Figure 1 shows how quantitative perfusion analysis may integrate into clinical practice.

Reviewer #2: This short 'how to' is well written, has a good flow and mentions all relevant topics. However, in its current form it neither sufficiently explains what is to be done (e.g., 'Verification of adequate stress can be achieved by reviewing the patient's symptoms, heart rate and systolic blood pressure response during the study as well as the presence of splenic switch-off if adenosine has been used as the stressor.'). What specifically has the user to do? Which symptoms, which cut-off for heart rate or blood pressure? How to do and how to interpret splenic switch off? In the end, the experienced reader does not learn anything novel, and the novice cannot use it for guidance. If space does not permit to explain in more detail, then at least some citations should guide towards more in depth reading. I would rather see citations for further reading than citations towards the small available evidence.

Response: We thank the reviewer for their positive comments. We have added clearer information and changed our references for further reading. We have added these sentences: “Verification of adequate stress is typically achieved by reviewing the patient’s symptoms (flushing, breathlessness and chest tightness), heart rate response (rise of ≥ 10bpm), systolic blood pressure (fall of >10mmHg) during the study and splenic switch-off on the acquired stress-images (2). However, this should not be used in isolation, and certain patient groups, particularly heart failure patients, may have a blunted haemodynamic response.” We have also included this reference on splenic switch-off:

Manisty C, Ripley DP, Herrey AS et al. Splenic switch-off: a tool to assess stress adequacy in adenosine perfusion cardiac imaging. Radiology 2015;276(3):732–740

Possible pitfalls should also be described, e.g. position of the input function, prebolus too small, too large, how to deal with black rim artefacts, how to discriminate 3VD from microvascular disease.

Response: Agreed and done.

We have added this paragraph on dark rim artefacts: “Dark rim artefacts affect the diagnostic accuracy of CMR perfusion and can mimic subendocardial perfusion defects leading to false positive diagnosis of CAD. Using quantitative perfusion CMR, MBF is generally lower in true perfusion defects compared to dark rim artefacts but may remain a source of error.”

We have added this sentence and reference regarding how to discriminate 3VD from microvascular disease: “Disease extent: Visual read of myocardial perfusion CMR compares signal changes between different myocardial regions and is thus adjusted for the lowest perfused area in an image, potentially masking less severe defects elsewhere. Quantitative analysis provides objective absolute blood flow values for each region. This is advantageous in multi-vessel CAD, where quantitative myocardial perfusion CMR better identifies disease extent than visual read (4).”

A discussion of positioning of the AIF is beyond the scope of this 'How to' article. We have included this sentence: "The AIF is typically taken from the basal LV but other sampling locations such as the ascending aorta have been proposed."

A discussion of optimal pre-bolus dose is beyond the scope of this paper. We have added this sentence regarding pre-bolus: "In the 'dual bolus' method a dilute bolus of contrast agent (typically 1/10 concentration of the full concentration bolus) is injected for LV blood pool analysis, followed by a full concentration bolus for myocardial analysis."

How to do Quantitative Myocardial Perfusion CMR

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Introduction

Myocardial perfusion cardiovascular magnetic resonance (CMR) using first pass contrast enhanced imaging is an established non-invasive test for the detection of myocardial ischaemia. Current practice involves visual interpretation of a series of dynamic images and relies on experienced reporters to identify perfusion defects. The acquired data can be used to derive quantitative maps of myocardial blood flow (MBF). Potential advantages over visual reading include: removal of operator dependence, simpler and faster analysis and the ability to detect disease with global rather than regional reduction of MBF. Recent developments allow semi-automated or fully-automated in-line calculation of MBF. Although these methods remain mostly in the research domain, they are on the threshold of becoming integrated into routine clinical care. This 'How to' article gives a brief practical overview of the steps involved in generating quantitative MBF maps and suggests how these may be used in clinical practice. This article is not intended as an exhaustive review of the principles or clinical evidence, which have been summarised elsewhere (1).

General principles

Myocardial perfusion CMR acquires a dynamic series of images immediately after injection of a T1-shortening gadolinium based contrast agent (GBCA). At least three myocardial short axis slices are acquired, every 1-2 heartbeat(s) typically over 40-60 seconds using a T1-weighted dynamic pulse sequence. The in-plane spatial resolution should be at least $2.5 \times 2.5 \times 10 mm^3$, achieved by fast imaging techniques such as fast gradient echo imaging or steady-state free precession (SSFP).
From these images, signal intensity profiles are taken from the left ventricular (LV) blood pool (to provide the arterial input function (AIF)) and the LV myocardium (which provides the tissue response). After conversion of dynamic MR signal changes to gadolinium (Gd) contrast agent concentrations for the AIF and myocardium, quantitative perfusion assessment can be performed using a number of different models, providing MBF values in units of millilitres of blood per minute per gram of tissue. Table 1 demonstrates steps to performing quantitative perfusion CMR.

Contrast agent dose and delivery

For visual interpretation of myocardial perfusion CMR images, a dose of 0.05 – 0.1mmol/kg GBCA is generally recommended to optimise signal changes in the myocardium. Quantitative perfusion CMR additionally requires measurement of signal in the LV blood pool, where concentration of GBCA is severalfold higher than in the myocardium and no longer linearly related to signal intensity. Uncorrected, this leads to miscalculation of MBF. To overcome this problem, in the 'dual bolus' method, a dilute bolus of contrast agent (typically 1/10 concentration of the full concentration bolus) is injected for LV blood pool analysis, followed by a full concentration bolus for myocardial analysis. In the 'dual sequence' method, images of the LV blood pool are acquired interleaved with the myocardial images following a single contrast bolus, but using a separate, less T1-sensitive pulse sequence, which avoids signal saturation. Once available outside of research settings, the dual sequence method is likely to integrate better into clinical workflow than the dual bolus method.

Baseline corrections

In order to allow reliable modelling of quantitative perfusion and comparison between myocardial segments, raw signal intensity data need to be corrected for baseline signal and surface coil inhomogeneities. This is typically achieved using proton density weighted images or myocardial T1 mapping preceding the acquisition of perfusion data.

Respiratory motion correction

Reliable quantitative perfusion analysis mandates elimination of bulk cardiac motion, usually achieved by breath-holding. However, long breath-holds can cause involuntary diaphragmatic drift and changes in heart rate. Furthermore, during pharmacological stress, patients may be unable to hold their breath

reliably. These problems can be overcome by free-breathing acquisition methods with correction of bulk cardiac motion ('rigid models') or more complex non-rigid deformation methods. As all motion correction methods can introduce artefacts, clinicians should always review both raw and motion corrected images.

Modelling

After the dynamic images are corrected for baseline signal and respiratory motion, signal intensity profiles are derived for the AIF and the myocardium using manual or automatic contouring. The AIF is typically taken from the basal LV but other sampling locations such as the ascending aorta have been proposed.

Endocardial and epicardial contours define the myocardium and further analysis can be on a global, segmental or pixel basis. AIF and myocardial signal intensity profiles are converted to GBCA concentration time curves. Several mathematical models such as the Fermi function have been proposed for the final step of quantification of MBF, each with specific advantages and limitations that are beyond the scope of this paper but have been reviewed elsewhere (1).

Interpretation and pitfalls of quantitative myocardial perfusion

The results of MBF quantification can be displayed at a segmental or pixel level with colour coding representing the magnitude of MBF. Rest and stress myocardial perfusion data are analysed separately to derive both rest and stress MBF. The ratio of stress/rest MBF defines the myocardial perfusion reserve (MPR), which can be displayed as a further polar plot. Further outputs from the analysis may include the AIF, myocardial signal intensity profiles and other data that can be used for quality assurance.

A reduction in stress MBF or MPR implies either coronary artery disease (CAD) or coronary microvascular dysfunction (CMD), but can also be caused by inadequate stress. Verification of adequate stress is typically achieved by reviewing the patient's symptoms (flushing, breathlessness and chest tightness), heart rate response (rise of ≥ 10bpm), systolic blood pressure (fall of >10mmHg) during the study and splenic switch-off on the acquired stress-images (2). However this should not be used in isolation, and certain patient groups, particularly heart failure patients, may have a blunted haemodynamic response.

Dark rim artefacts affect the diagnostic accuracy of CMR perfusion and can mimic subendocardial perfusion defects leading to false positive diagnosis of CAD. Using quantitative perfusion CMR, MBF is generally lower in true perfusion defects compared to dark rim artefacts, but may remain a source of error.

Registration, segmentation and other errors may lead to erroneous MBF maps and automated and manual quality checks should be a routine part of quantitative myocardial perfusion imaging interpretation.

Potential integration of quantitative perfusion into clinical reporting

No current guidelines exist on how to integrate quantitative myocardial perfusion CMR into clinical reporting and on how to combine it with visual analysis. As the bulk of the existing evidence for myocardial perfusion CMR is for visual analysis, this should continue to form the principal analysis strategy. Quantitative perfusion maps may supplement visual interpretation in several ways:

1. Confirmation of visual read: Successive or simultaneous visual and quantitative analysis may enhance diagnostic certainty where the two strategies agree and, when results are discrepant, may alert the reader to ther presence of artefacts.

2. Adequacy of haemodynamic response: When inadequate haemodynamic response is suspected based on a lack of clinical response or absence of splenic switch off, review of quantitative perfusion maps can help confirm (low stress MBF and/or MPR) or refute (high stress MBF and/or MPR) this suspicion.
3. Suspected Coronary Microvascular Dysfunction (CMD): Visual interpretation of myocardial perfusion CMR has limited ability to detect CMD. In patients with no regional visual perfusion defects and adequate haemodynamic response, but low stress MBF or MPR on quantitative myocardial perfusion mapping, CMD is a likely diagnosis. Thresholds for diagnosing CMD with quantitative myocardial perfusion CMR have been proposed in small studies but have not been widely validated and may not be applicable across different acquisition methods (3).
4. Disease extent: Visual read of myocardial perfusion CMR compares signal changes between different myocardial regions and is thus adjusted for the lowest perfused area in an image, potentially masking less severe defects elsewhere. Quantitative analysis provides objective absolute blood flow values for each region. This may be advantageous in multi-vessel CAD, where quantitative myocardial perfusion CMR may better identify disease extent than visual read (4).
5. Follow up studies and research: Quantitative myocardial perfusion CMR provides absolute numbers of MBF, which can help assess treatment effects.

Figure 1: Potential scenarios when Quantitative Perfusion analysis may integrate into clinical practice

In a patient with visually homogenous perfusion, normal stress MBF/MPR by quantitative perfusion (QP) can reaffirm the diagnosis of a normal perfusion study. Conversely, visually homogenous perfusion with low stress MBF/MPR suggests either inadequate vasodilatory response (check splenic switch off and haemodynamic response), coronary microvascular disease (which may show an endo to epicardial perfusion gradient) or severe triple vessel disease (where the pattern of perfusion is typically heterogenous). In a patient with a regional perfusion defect on visual analysis, QP may help

identify the extent of disease (visual analysis is relative and may underestimate disease extent) and peri-infarct ischaemia.

Automated in-line quantitative perfusion mapping

Historically, calculation of quantitative perfusion has been laborious, requiring manual contouring of hundreds of images, exporting data to external computers and manual analysis of the data with locally developed post processing tools. This has prevented the use of quantitative CMR perfusion in routine clinical care. Recently, fully automatic in-line methods that include motion correction, automatic detection of the AIF, segmentation of the myocardium and pixel-wise calculation of MBF have been proposed (5). Artificial intelligence can deliver automatic segmental and global quantification, allowing precise, rapid large-scale analysis. Such automated analysis pipelines can be integrated into the scanning acquisition to deliver quantitative perfusion maps in-line or immediately after data acquisition.

Future Directions

Large, multicentre prospective randomised-controlled studies are needed to further explore the prognostic value of quantitative myocardial perfusion CMR and its ability to guide revascularisation decisions. The most effective integration of quantitative perfusion into clinical pathways needs to be defined. Despite emerging consensus on the methodology, a number of different approaches to quantitative myocardial perfusion CMR are currently in use and international standardisation is needed.

References

1. Quinaglia T, Jerosch-Herold M, Coelho-Filho OR. State-of-the-Art Quantitative Assessment of Myocardial Ischemia by Stress Perfusion Cardiac Magnetic Resonance. Magn Reson Imaging Clin N Am. 2019 Aug;27(3):491-505
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Table 1

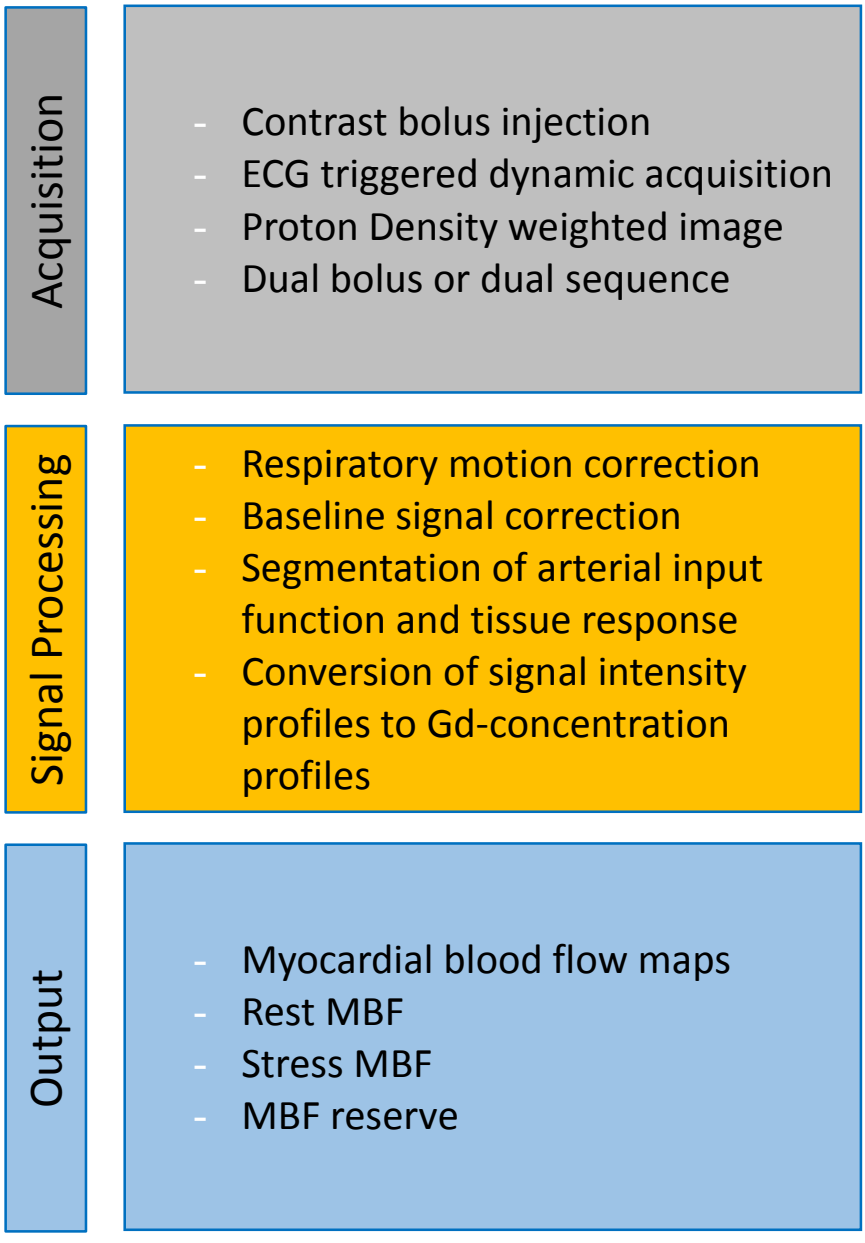

Table 1 : Steps to performing quantitative myocardial perfusion. MBF refers to myocardial blood flow.

Word Count

How to do Quantitative Myocardial Perfusion CMR

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Figure 1